

RICE UNIVERSITY

**Catalytic Organosilane Activation with Copper Complexes**

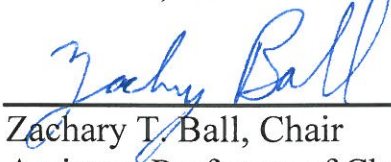
by

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A THESIS SUBMITTED  
IN PARTIAL FULFILLMENT OF THE  
REQUIREMENTS FOR THE DEGREE


**Doctor of Philosophy**

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## Abstract

### **Catalytic Organosilane Activation with Copper Complexes**

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The development of reactive organometallics has become a vital part synthetic chemistry. Organosilanes potentially represent a cheap, robust, and environmentally benign precursor to reactive organometallics, but the nature of the very stable C–Si bond has generally prevented their use as precursors to more reactive organometallics. We present investigations into copper fluoride complexes which activate organosilanes in anhydrous media under mild conditions, effecting transmetalation to produce stable and in some cases isolable organocopper species containing sensitive functional groups including carbonyl groups, aryl bromides, benzylic chlorides, and alkyl ketones. This discovery allows us to better understand the fundamental reactivity of presumed intermediates in copper-catalyzed reactions and to develop new catalytic bond-forming processes including allylations of aldehydes, 1,4-addition of vinyl epoxides, and intramolecular ring closures.

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Jessica Herron

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# Abbreviations

## **Instrumentation:**

GC-MS	Gas Chromatography-Mass Spectrometry
NMR	Nuclear Magnetic Resonance Spectroscopy
RI-NMR	Rapid Injection Nuclear Magnetic Resonance Spectroscopy

## **Materials:**

Bipy	2,2'-Bipyridine
bod	bicycle[2.2.2]-octa-2,5-diene
cod	cyclooctadiene
cp*	pentamethylcyclopentadiene
dba	dibenzylideneacetone
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
IPr	1,3- Bis(2,6,2'-diisopropylphenyl)imidazol-2-ylidene
NBD	Norbornadiene
NHC	N-Heterocyclic Carbene
NMP	N-Methyl-2-Pyrrolidone
SICy	Dicyclohexylimidazolin-2-ylidene
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate



TBAF	Tetrabutylammonium fluoride
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TMAF	Tetramethylammonium fluoride
TMSCN	Trimethylsilyl cyanide
VTMS	Vinyltrimethylsilane

**Other:**

aq	aqueous
ee	Enantiomeric Excess

# Chapter 1

## Generation of reactive organocopper species

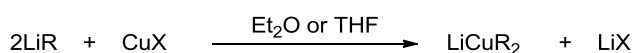
### 1.1 Introduction

The development of new active pharmaceutical ingredients, diversity-oriented synthesis of libraries of molecules, and the discovery of new materials situate synthetic methodology as a central discipline in science. To address synthetic demands, transition metal catalysts have been introduced to the field of organic chemistry, leading to a revolution in how chemists approach the synthesis of complex organic molecules. The interest in transition metals results from the complex and unique transformations observed in ligand exchange,<sup>1,2</sup> oxidative addition,<sup>3</sup> and carbonylations.<sup>4</sup> Some of the most powerful transformations in organometallic chemistry have involved copper(I)-promoted carbon-carbon bond forming reactions<sup>5</sup> such as conjugate addition,<sup>6</sup> carbometalations,<sup>7</sup> mild epoxide openings,<sup>8</sup> and clean S<sub>N</sub>2 substitutions.<sup>9</sup> The rich history of organocopper(I) dates back to 1859,<sup>10</sup> but it was not until 60 years later that Reich reported the isolation of phenylcopper from the reaction between CuI and phenyl Grignard;<sup>11</sup> such monoorganocopper reagents have limited thermal stability and moderate reactivity. New discoveries allowed chemists to reveal useful copper mediated transformations for synthesizing complex target molecules.

A major breakthrough came in 1952 with the discovery of the Gilman cuprate,<sup>12</sup> namely lithium dimethylcuprate, which was prepared by the reaction with methyl copper (which has very

poor solubility) and methyl lithium. After discovering dialkyl cuprates could be generated by adding the desired copper salt to two equivalents of the organolithium reagent (Scheme 1), a wealth of copper promoted reactions surfaced.<sup>9,13</sup>

### Scheme 1. Synthesis of Gilman cuprate



This chapter is organized into four sections. The first section (1.2) discusses the reactivity of organocopper compounds. Next, (1.3) the generation of organocopper compounds via transmetalation with other organometallic species (Li, Mg, Zn, B, Sn, Si) will be discussed. Lastly, (1.4) the mechanistic aspects of nucleophilic copper(I) chemistry will be presented leading up to the ability to transition from stoichiometric organocopper reagents to catalytic amounts of copper additives.

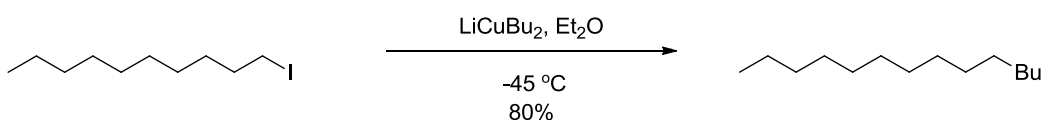
## 1.2 Copper-promoted synthetic transformations

### 1.2.1 S<sub>N</sub>2, epoxide opening, reactions with acyl halides

Organocuprates are well-suited for substitution reactions (Scheme 2) on a wide range of saturated and unsaturated electrophiles such as haloalkanes,<sup>9</sup> as well as their allylic and propargylic derivatives.<sup>14</sup> Corey and House explain that organolithium reagents appear weakly nucleophilic towards electrophilic carbons in this case, rather acting as a base promoting, 1,2-

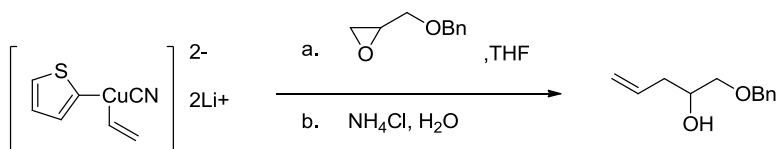
elimination or undergoing a lithium-halogen exchange. They also describe organomagnesium reagents as unreactive in the case of performing the desired alkylation reaction.<sup>15</sup>

**Scheme 2. Addition reaction of an organocuprate to an alkyl iodide<sup>15</sup>**



Cuprates are among the mildest and most efficient reagents available for epoxide opening in comparison to their organolithium precursors.<sup>16,17</sup> In the case of substituted oxiranes, good regioselectivity is observed with nucleophilic addition occurring at the less sterically hindered carbon of the oxirane ring. The example shown below (Scheme 3) also highlights advancement in organocopper chemistry: higher order cuprates. Organocopper species bearing three anionic groups are termed “higher order” cuprates. It was reported in 1973 that “higher order” cuprates possess increased reactivity and selectivity in comparison to lower order cuprates.<sup>5</sup>

**Scheme 3. Mild epoxide opening with higher order mixed cuprate<sup>18</sup>**

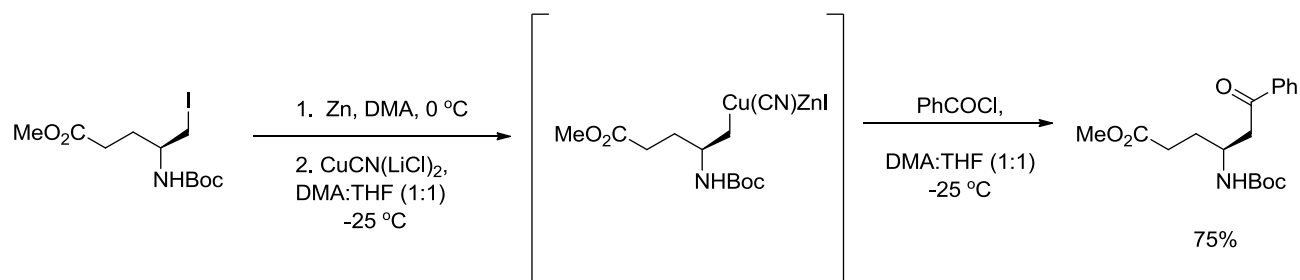


An additional highlight of Scheme 3 is the advent of the dummy ligand.<sup>19</sup> In the case of homocuprates (Gilman reagents), two equivalents of the coupling group are required for the

cuprate synthesis. This process is wasteful since one equivalent is essentially lost. This may be of little concern if the coupling agent is commercially available, but quite often the coupling segment is expensive or a product of lengthy chemical synthesis. Losing one equivalent of these materials can be distressing. Methods to suppress the loss of one of the transferable groups are implemented with the use of a mixed complex. In this case, incorporating both 2-thiophenyl and cyano ligands as non-transferable groups prevents the wasteful nature of Gilman reagents. It is assumed that  $d\pi^*$  backbonding from the Cu(I) to the alkynyl and cyano ligands (Scheme 3) accounts for their limited transfer rates from cuprates.

Organocuprates will also react with acylchlorides producing ketones without concomitant nucleophilic attack to the resulting ketone as seen in the case of Grignard and organolithium reagents.<sup>20,21</sup> Tanner and coworkers studied the convergent synthesis of ketones using copper-mediated cross-coupling of an alkyl iodide and an acid chloride (Scheme 4). Insertion of zinc into the alkyl iodide, followed by transmetalation with copper led to the corresponding copper-zinc species, which was added to benzoyl chloride. This methodology complements the Pd(0)-catalyzed addition of organozinc halides to acid chlorides, and in cases where low or no yields are obtained. The zinc to copper methodology offers similar yields to the iron mediated reaction of Grignard reagents with acyl chlorides.<sup>22</sup> The zinc to copper transmetalation methodology may be useful in gaining access to the desired products where transmetalation will not occur with palladium and functional-group-tolerance is not present with Grignard reagents.

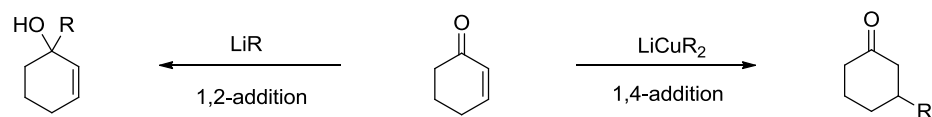
**Scheme 4. Copper-mediated addition of organozinc halides to an acid chloride<sup>20</sup>**



**1.2.2 Conjugate addition**

Tawney and Kharasch discovered an interesting feature of this class of compounds in 1941 when they treated 2-cyclohexenone and methylmagnesiumbromide with a catalytic amount of copper(I) chloride.<sup>6</sup> They observed mostly (82.5%) 1,4-addition, in contrast to 1,2-addition that is observed with the Grignard reagent alone (Scheme 5). Analogous reactions between these substrates and  $\text{RMgX}$ , similar to Tawney's discovery, have also been described.<sup>23</sup>

**Scheme 5. Regioselectivity of organocuprates with  $\alpha,\beta$ -unsaturated ketones**

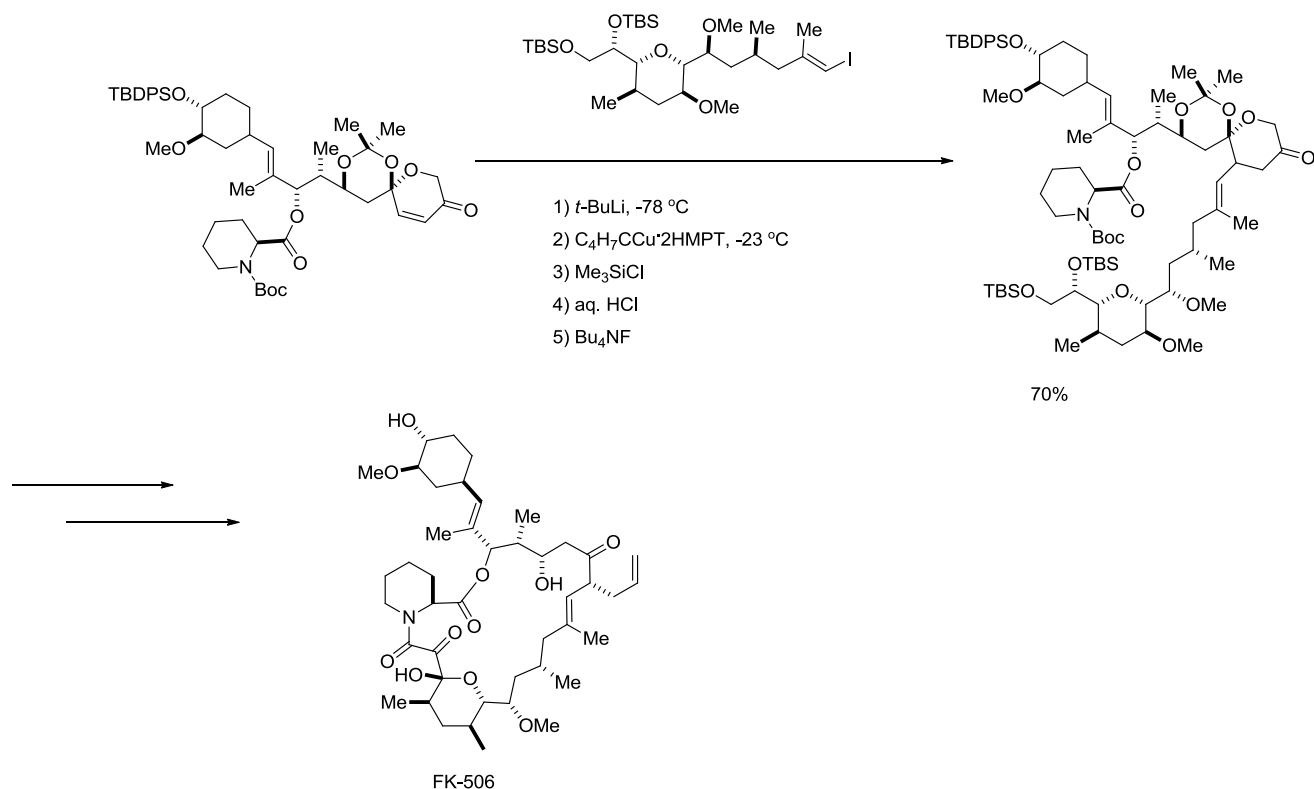


Following these early reports, research in this area flourished, and the frequent application of this methodology in total synthesis of natural and unnatural products demonstrated

the versatility of this reaction.<sup>24</sup> The versatility of the conjugate addition is mainly due to the large variety of potential nucleophiles and acceptors. A wide range of functional groups can be incorporated into the haloalkane component without need for protection: alkene, ester, amide, nitrile, ketone, sulfonamide, as well as most popular protecting groups, are tolerated remarkably well.

Late stage carbon-carbon bond formation in target-oriented synthesis can be quite challenging. Use of mild, functional-group-tolerant methodology is necessary to introduce carbon-carbon bonds to multifunctional molecules. A noteworthy example, employing organocopper chemistry, is shown below in the synthesis of immunosuppressant FK-506 (Scheme 6).<sup>25,26</sup> Towards the end of the synthesis of the target compound, the nucleophilic partner exhibits a complex core, containing several stereocenters, and protecting groups. The electrophilic partner contains many groups incompatible with other organometallic compounds. After generation of the functionalized organocopper complex, addition to the electrophile proceeds selectively performing a 1,4-addition to the  $\alpha,\beta$ -unsaturated carbonyl. Other transition metal-promoted 1,4-addition reactions available at this time would likely react with the other olefin in the molecule as well.

### Scheme 6. Synthesis of FK-506<sup>26</sup>

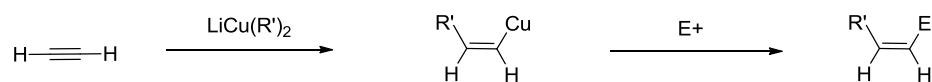


Great emphasis has been put on the development of catalytic tools. The copper-catalyzed conjugate addition of organometallic reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds has received a great deal of attention over the years and has made significant contributions to the field. Highly efficient and easy to use catalytic systems have been developed so that the organic chemist can now select a suitable ligand for the desired chemical transformation.<sup>27</sup> Chiral copper complexes make enantioselective versions of these reactions possible. Some of these examples will be discussed in later sections of this chapter.



### 1.2.3 Carbocupration

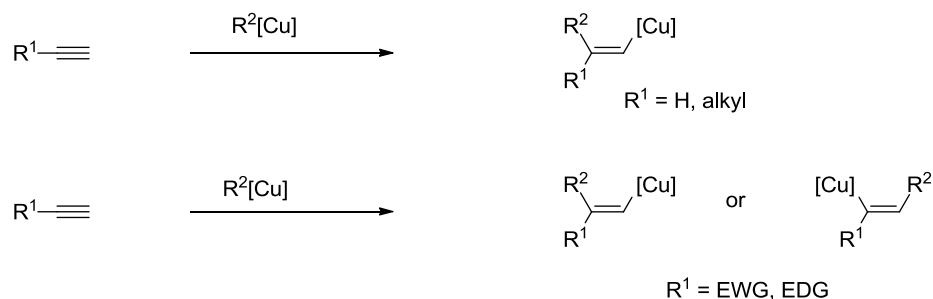
**Scheme 7. Carbocupration of acetylene**



The stereoselective synthesis of multifunctional alkenes within a single reaction flask remains a challenging task for organic chemists. Many metals undergo carbometalations. The addition of organocopper reagents to alkynes is one of the most useful carbometalation reactions (Scheme 7), as it allows the straightforward synthesis of stereodefined alkenyl copper reagents.<sup>28</sup> Therefore, carbocupration represents a powerful tool for the stereoselective preparation of di-, tri- and tetra-substituted olefins. The reactions can be conducted with various organocopper reagents including organocopper species from Grignard reagents, Gilman-type cuprates, and organocopper-zinc mixed species.<sup>7</sup> The carbocupration reaction occurs in most cases in a strictly syn-addition pathway.

The regioselectivity is related to the substitution pattern of the alkyne partner (Scheme 8). With acetylene and simple monosubstituted alkylalkynes, the addition leads to the less substituted alkenyl copper species. However, the presence of a donor or acceptor group on the acetylenic moiety or near the acetylenic moiety can interfere with this general pattern and lead to a different regioselectivity.

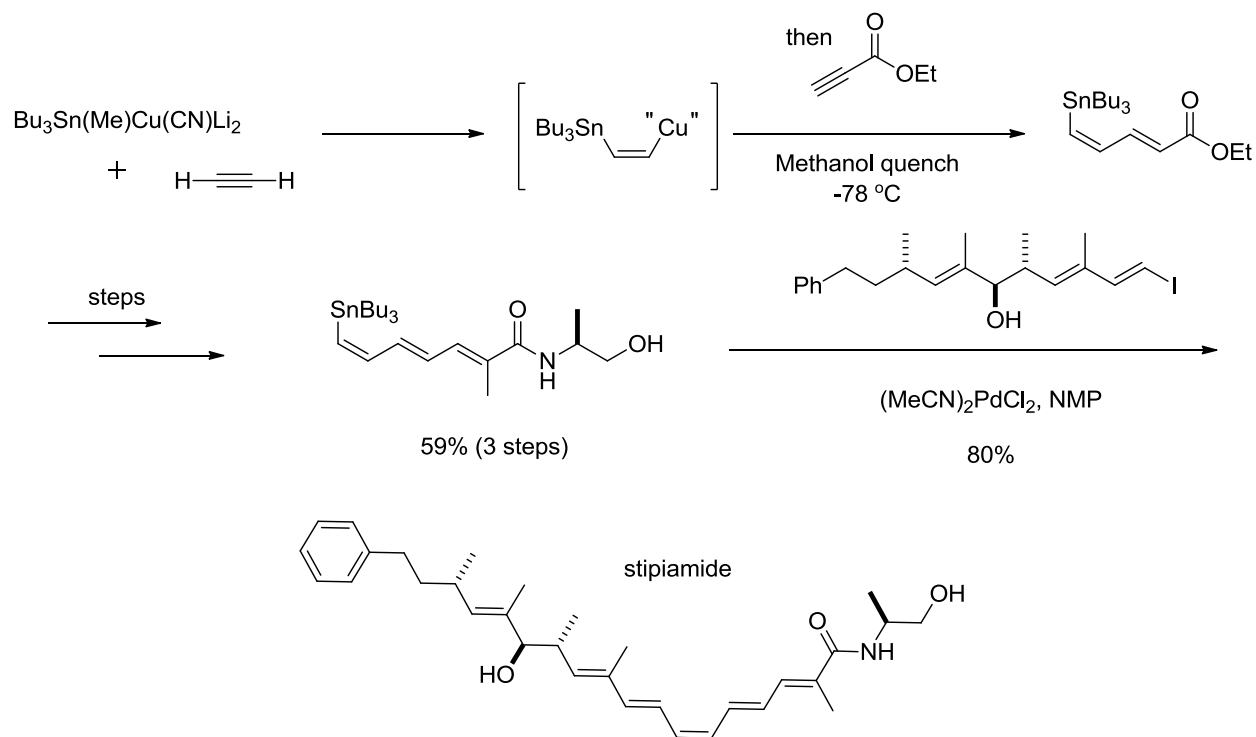
### Scheme 8. Regioselectivity of carbocupration



The resulting vinylcopper species can be trapped with a range of electrophiles including, but not limited to, alkyl halides, enones, carbon dioxide, iodine, aldehydes to produce a single olefin isomer. The ability to perform carbometalation makes the organocopper reagent an indispensable tool; allowing access to target structures that would otherwise have no previous synthetic route. The main field of application is related to the total synthesis of insect pheromone, as numerous pheromones present one or more disubstituted alkene functionalities with a specific (*E*)- or (*Z*)-configuration.<sup>29-31</sup>

Copper-mediated introduction of heteroatoms such as stannyl groups have frequently been used in place of carbon units as a strategy to construct key precursors in synthesis. Using sequential tin-copper syn additions of tributylstannyl cuprate to acetylene, followed by conjugate addition of ethyl propionate allowed the synthetic construction of stipiamide (Scheme 9), a member of a growing class of insecticidal polyene antibiotics possessing anti-HIV and antifungal activities.<sup>32</sup>

### Scheme 9. Synthesis of stipiamide<sup>32</sup>



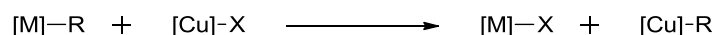
Copper-mediated transformations have undergone an interesting development during the last several years. So far, very little has been discussed (in this chapter) on ways to perform these reactions in an atom economical way. In the next section, generation of organocopper species through a variety of transmetalation reactions will be discussed including recent developments in copper catalysis.

### 1.3 Generation of organocopper compounds via transmetalation

Organocopper compounds are frequently generated via transmetalation with other organometallics. Transmetalation is generally described as an exchange of ligands between two metal centers (Scheme 10). The ligands that are exchanged can be either organic or inorganic.

Most commonly, organo-lithium reagents are used to generate organocopper reagents, but organomagnesium as well as a variety of other organometallic species may, be transmetalated with a copper halide. All organometallics in which the metal is less electronegative than copper, and all organometallic species of similar electronegativity but weaker carbon-metal bonds, are potential candidates for transmetalation reaction. Aside from organo-lithium and -magnesium reagents, organo-boron, -aluminium, -zinc, -tin, -lead, -tellurium, -titanium, -manganese, -zirconium, -samarium, and -silicon have all been found to transmetalate with copper compounds, resulting in a wide range of reactive organocopper species. In this section, transmetalation reactions involving lithium, magnesium, zinc, boron, tin, and silicon will be discussed. Detailed discussion of the generation of reactive copper intermediates from the other metals that will not be covered in this chapter have been thoroughly reviewed.<sup>33</sup>

#### **Scheme 10. Transmetalation**



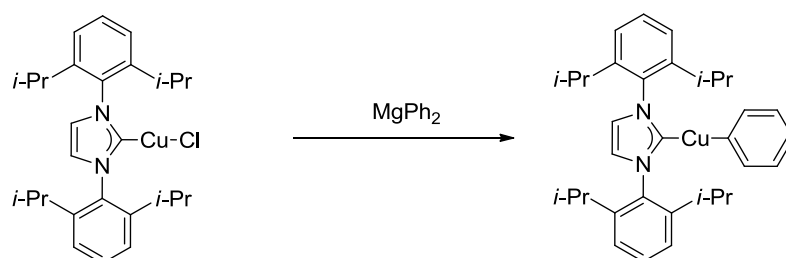
##### **1.3.1 Transmetalation of organolithium and organomagnesium**

Organocopper reagents are desired due to their high reactivities and chemoselectivities. As mentioned before, most often organocopper reagents are generated from organolithium and –magnesium precursors. These reactive precursors alone are often incompatible with organolithium and magnesium reagents. By generating the copper reagent first, access to transformations such as conjugate addition in and carbometalations are permitted. This method

has provided a plethora of amazing transformations, allowing access to total synthesis routes that were not available as seen in previous examples in this chapter.

Whereas stoichiometric organocopper reactions usually proceed best when the cuprates are derived from organolithium reagents, catalytic reactions normally involve Grignard reagents<sup>23</sup> (which also have the added benefit of being easier to prepare, and the ability tolerate additional functionality). Many enantioselective transformations have been achieved by employing a chiral ligand for copper. A major contribution to the area has been made through the emergence of N-heterocyclic carbene (NHCs) ligands.<sup>34</sup> Quite often ligands are used to support solubility and stabilize copper compounds that would thermally decompose (sometimes violently). As discussed in section 1.1, phenylcopper is thermally unstable and difficult to isolate. When an NHC ligand is employed (Scheme 11), in the case of IPr (IPr = 1,3-bis(2,6,2'-diisopropylphenyl)imidazol-2-ylidene), not only does the copper reagent have improved solubility, it is also thermally stable at room temperature.<sup>35</sup>

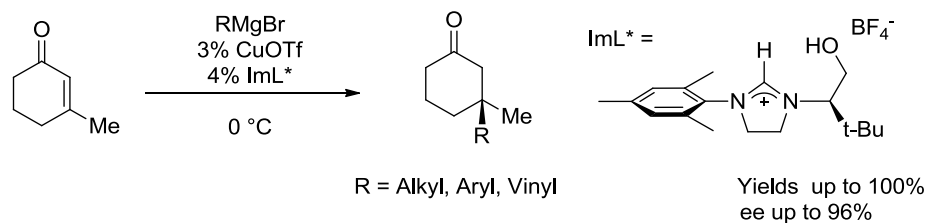
**Scheme 11. Generation of (IPr)CuPh<sup>35</sup>**



Alexakis and coworkers have taken advantage of carbene ligands, which they directly generate in situ.<sup>36</sup> In their report, copper-catalyzed asymmetric conjugate addition of Grignard reagents to trisubstituted cyclic enones affords all-carbon quaternary centers in excellent yields

and enantiomeric excess (Scheme 12). Previous to this report the addition of a phenyl group on enones with this substitution pattern, could not be achieved by other conjugate addition methods. This example stands out as a significant contribution to the field of copper-catalyzed asymmetric conjugate addition, but a noteworthy drawback to this work is the lack of functional-group-tolerance in regard to the reactive organometallic reagent. As mentioned in other sections, when precursors are species as reactive as Grignard reagents, only relatively unfunctionalized organocopper reagents may be prepared.

**Scheme 12. Copper-catalyzed conjugate addition of Grignard reagents to 3-substituted cyclohexenones<sup>36</sup>**



With the lack of functional-group-tolerance with regard to copper reagents, other transmetalation partners have been explored. In the next sections, milder approaches to functionalized organocopper species will be discussed.

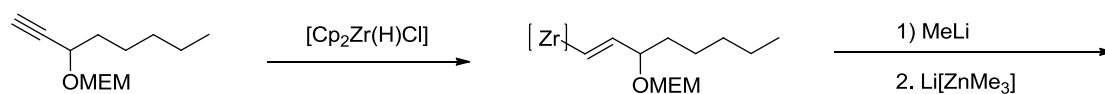
### 1.3.2 Transmetalation of organozinc compounds

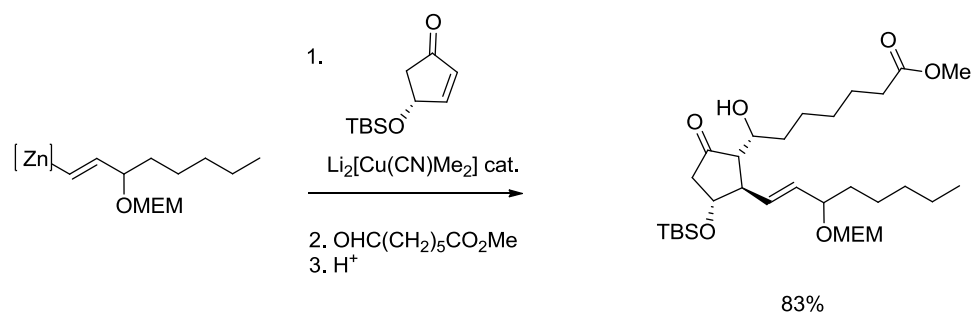
A disadvantage of the classical method of preparation is that the organolithium and Grignard reagents required are too basic and nucleophilic to be compatible with most functional groups. This method can therefore provide only cuprates containing simple, unfunctionalized

groups. One solution to this problem is conducting the transmetalation reaction with less reactive organometallics. Organozincs undergo smooth transmetalations to give a broad range of organometallics.<sup>37,38</sup> Transmetalation to organocopper compounds proved to be particularly important since it is possible to prepare organozinc compounds bearing a range of organic functional groups.<sup>39</sup> This high functional group tolerance results from pronounced covalent character of the carbon-zinc bond, while the excellent transmetalation capability is a consequence of low-lying empty *p*-orbitals. After transmetalation, with organozinc reagents, the resulting organocopper species will react with most electrophiles including those that the more classical lithiumorganocuprates would.

Organocopper reagents prepared from organozinc species have been used to synthesize valuable targets in organic synthesis such as prostaglandins. In the synthesis of prostaglandin 12 three transmetalation steps are conducted with four different metals without isolation of the intermediates (Scheme 13).<sup>40-43</sup> The starting alkyne is converted with the Schwartz reagent into the vinylzirconocene. Methylation with MeLi and transmetalation with lithium trimethylzincate leads to the organozinc species. In the presence of catalytic quantities of the organocuprate, the resulting organocopper species undergoes 1,4-addition to a chiral enone which leads to a copper or lithium enolate that can be converted into the corresponding zinc enolate by transmetalation. The zinc enolate can then react with an electrophile to give the final product.

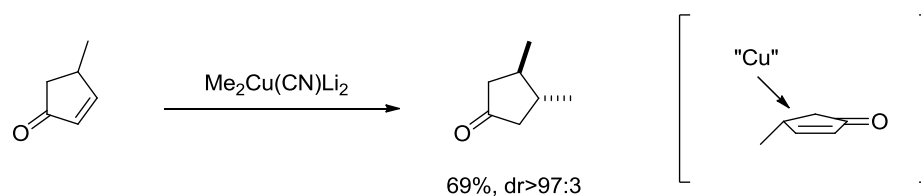
**Scheme 13. Synthesis of prostaglandin 12<sup>40</sup>**





This example illustrates the important concept of the diastereoselectivity of chiral cyclic systems (Scheme 14). The synthetic potential of the diastereoselective addition of organocopper reagents to Michael acceptors has been thoroughly summarized.<sup>44</sup> Cyclic systems usually adopt distinct preferred conformations, which frequently allow them to pass through a single reactive conformation in the course of a chemical reaction; this often results in a single product. In this context, addition of organocuprates to chiral, cyclic enone systems frequently occurs with high levels of stereoselectivity. Historically, this

#### Scheme 14. Diastereoselectivity of cuprates with chiral, cyclic enones<sup>44</sup>

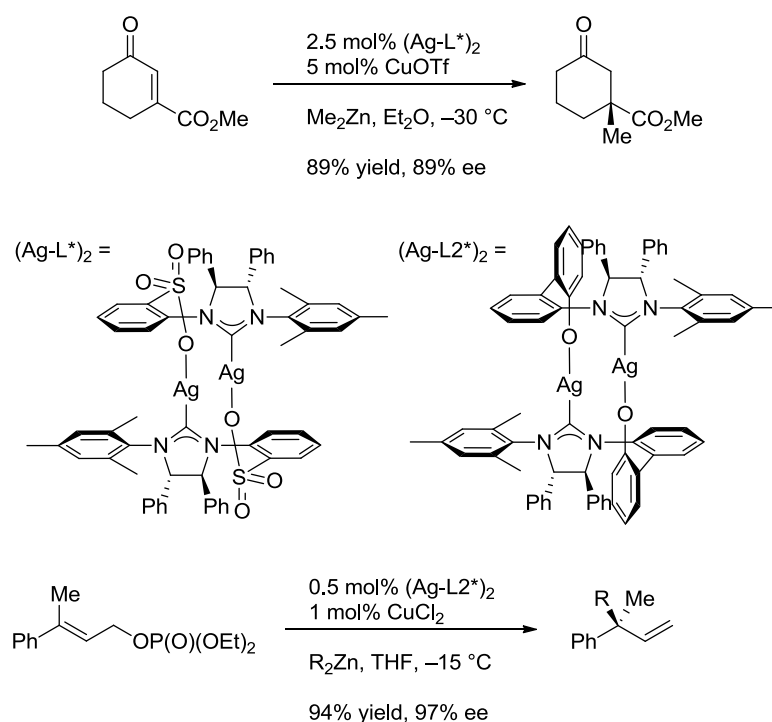


chemistry has had a major impact on the field of total synthesis of steroids and prostaglandins like the examples discussed above. Addition of the functionalized organocuprate reagent to the chiral cyclopentenone in Scheme 13 occurs in a trans selective fashion to give a zinc enolate. This enolate then proceeds in a stereoselective addition to an aldehyde resulting in the desired product.



Many copper-catalyzed diastereoselective reactions with stoichiometric amounts of organozinc reagents are present in the literature. As the need for synthetic methodology grows, copper-catalyzed asymmetric conjugate addition evolves and matures as a synthetic tool, allowing high yields and enantioselectivities on a general scope of substrates and a broad range of organometallic nucleophiles. The Hoveyda, Feringa, and Alexakis labs have been instrumental in introducing diaorganozincs as primary organometallics in the field of asymmetric conjugate addition. Again, they rely on NHC ligands to supply the chiral information needed to obtain such impressive enantiomeric excess in both activated and unactivated systems (Scheme 15).<sup>45,46</sup> In these examples, the NHC ligands afford an acceleration of the reaction rate as well.

**Scheme 15. Copper-catalyzed conjugate addition of organozinc reagents to 3-substituted cyclohexenones. Figure adapted from references 45 and 46.**

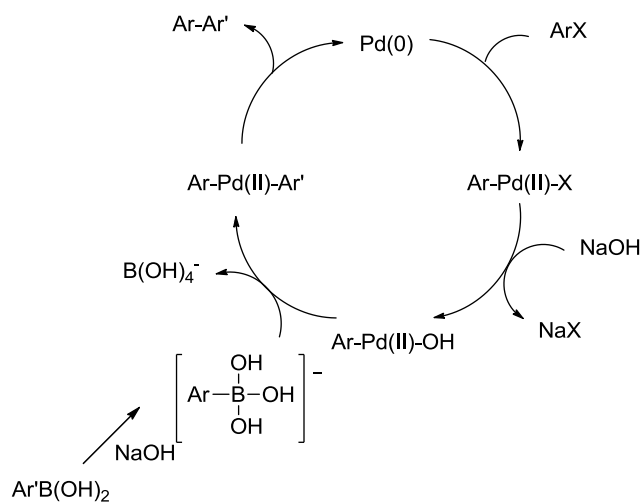


Unlike Scheme 12, the carbene ligand is transferred to copper by transmetalation with a dimeric silver(NHC) complex, presumably making the system more tolerant to air and moisture. While these examples are impressive, there is still room for the methodology to grow. The use of silver offers alternative transmetalation candidates that are potentially water and air stable and do not require temperatures below room temperature.

### 1.3.3 Transmetalation of Organoboron compounds

There are a variety of transition metal (Rh, Pd, Cu, etc...) catalyzed reactions involving a transmetalation step with organoboron reagents.<sup>47-49</sup> Organoboron reagents are best known for their nucleophilic role in Suzuki-Miyaura cross-couplings (Scheme 16).<sup>50-52</sup> The arylboron compounds employed in this reaction offer a variety of advantages, including ready accessibility, and ease of incorporation of nontransferable boron ligands; the relative nontoxicity of the byproducts generated upon cross-coupling make organoboron reagents a preferred nucleophilic partner. Recent catalyst and method

#### Scheme 16. Suzuki-Miyaura coupling reaction mechanism



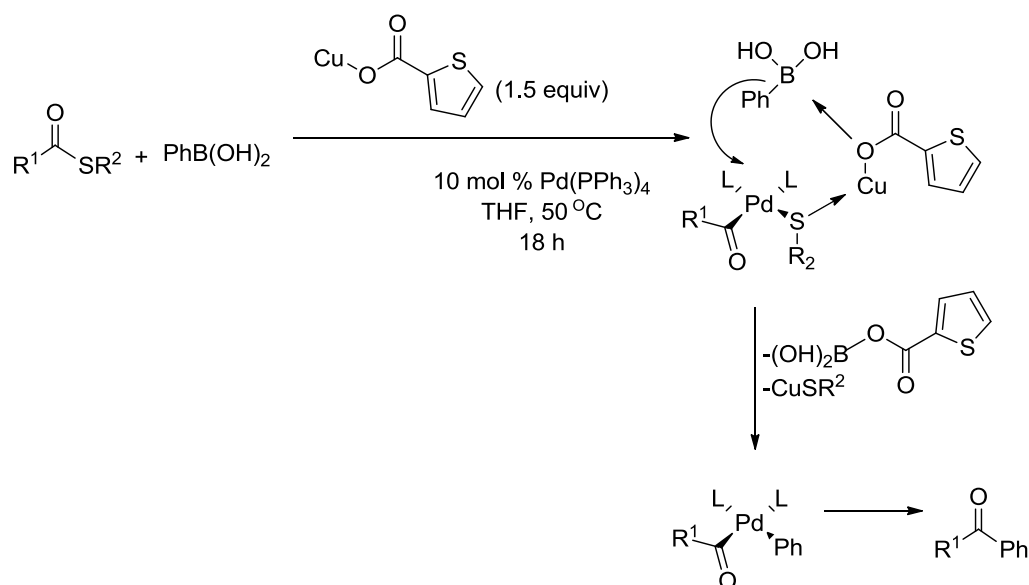
developments have broadened the possible applications enormously, so that the scope of the reaction of organoboron partners is not restricted to aryls, but also includes alkyls, alkenyls and alkynyls.<sup>53,54</sup> There is currently widespread interest in applications of the Suzuki Coupling, with new developments and refinements being reported constantly.

Using organoboron reagents as precursors to generate reactive organocopper species also has synthetic potential. Unlike organo-lithium, -magnesium, -aluminum, and -zinc compounds, organoboron reagents are often much easier to handle. Also, a variety of complex substrates can come from hydroboration of alkynes and alkenes. Except in the case of aryl substrates, this is one of the few examples where organohalides are not the precursors to functionalized organometallic species. Direct transmetalation of organoboranes to organocopper reagents is not a general reaction. Because of their similar bond energies and electronegativities, this transmetalation is limited to the preparation of alkenylcopper and unfunctionalized alkylcopper compounds. In the latter case, the reaction is favored by the formation of a boronate-complex, by adding an alkyl lithium reagent.<sup>55,56</sup> Better results can be obtained by generating the boronate species with the aid of sodium methoxide.<sup>57</sup> Satisfactory transmetalation occurs, furnishing the desired copper complex. Quite often, much more general access to organocopper compounds can be achieved by prior conversion of the organoboranes into organozinc compounds.<sup>21</sup> After this transmetalation, the organozinc reagents could then perform a more efficient transmetalation with copper.

Since these earlier reports that rely heavily on zinc, Liebeskind and coworkers have demonstrated a mechanistically unprecedented transition-metal-catalyzed cross-coupling of thioesters with boronic acids to produce ketones under neutral conditions (Scheme 17).<sup>58</sup> This desulfurative cross-coupling process is catalytic in palladium(0), stoichiometric in copper(I), and applicable to a range of organosulfur derivatives and nucleophilic organometallic reagents. A key feature of this method is the requirement of a stoichiometric amount of a copper(I) carboxylate species, such as copper(I) thiophene-2-carboxylate (CuTC), as a thiophilic metal cofactor. After

oxidative addition of the thioester to the Pd(0) catalyst, the copper(I) carboxylate serves the dual role of polarizing the Pd-S bond through Cu(I) coordination to the sulfur center and activating the trivalent boron compound simultaneously through coordination of the carboxylate to the boron center. A full equivalent of the Cu(I) additive is required because of the need to scavenge the released thiolate as the reaction proceeds.

**Scheme 17. Palladium-catalyzed, copper(I)-mediated Liebeskind-Srogl ketone synthesis. Figure adapted from reference 56.**

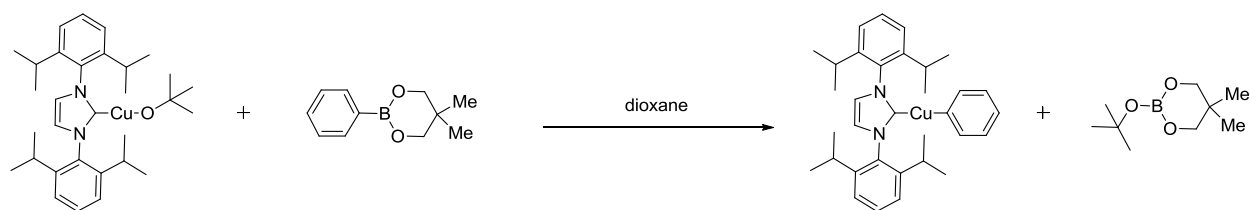


The synthesis of ketones from thioesters and boronic acids from this transformation is clearly an important addition to previously existing methods for ketone synthesis from carboxylic acids and their derivatives.

Hayashi and coworkers demonstrate direct transmetalation between arylboronic esters and  $(NHC)CuOt-Bu$  complexes (Scheme 18).<sup>59,60</sup> Again N-heterocyclic carbene ligands emerge as an outlet to access unique stability. In this case not only do they observe transmetalation, but the resulting copper aryl species can be isolated in analytically pure form. Unlike oligomeric

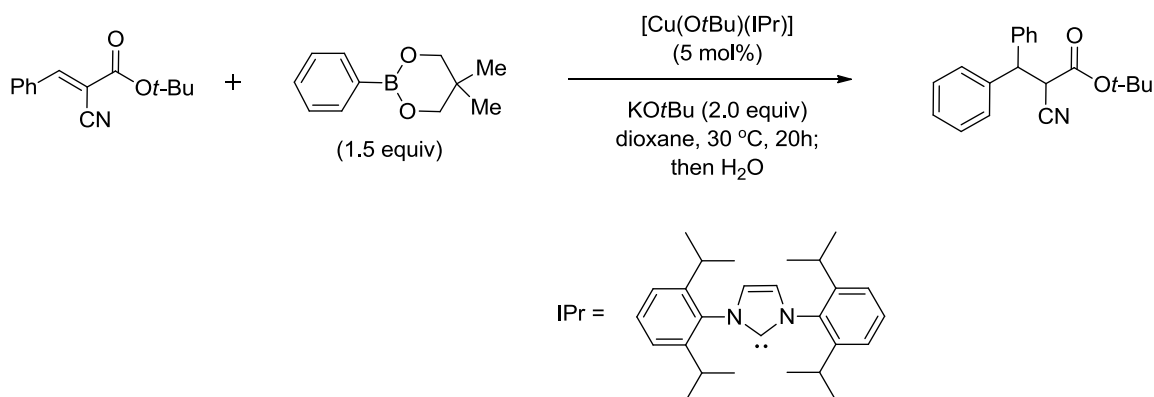
organocuprates, this neutral copper(I) compound is monomeric. The ease with which these compounds are isolated and characterized allows one to study and obtain mechanistic insights that might otherwise be difficult to study in the case of oligomeric and salt mixed cuprate species.

**Scheme 18. Boron to copper transmetalation. Figure adapted from reference 58.**



After confirming that the resulting copper aryl species react stoichiometrically with activated enolate substrates, Hayashi and coworkers demonstrated a method to perform the reaction with catalytic amounts of copper (Scheme 19). They rely on stoichiometric amounts of potassium *tert*-butoxide to activate the boronic ester and facilitate further boron to copper transmetalation. Like other methods mentioned in previous sections, when an achiral ligand is replaced with a chiral ligand, good enantioselectivities can be achieved. While this is a significant advancement, again we see this issue of large amounts of basic reagents making it difficult to obtain functionalized organocopper species bearing base sensitive functional groups, leaving room for development of boron to copper transmetalation based methodology.

**Scheme 19. Copper-catalyzed conjugate addition of organoboron reagents to  $\alpha,\beta$ -unsaturated enoates. Figure adapted from reference 58.**



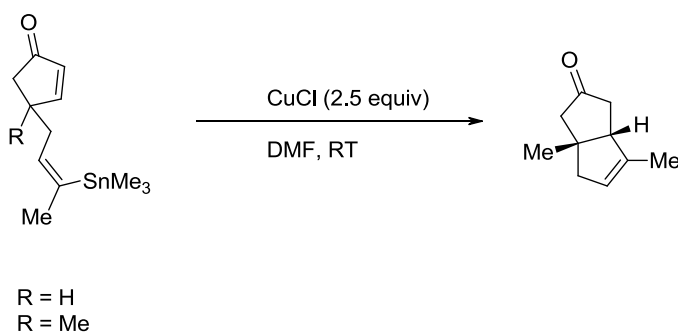
### 1.3.4 Transmetalation of organotin compounds

Although organotin compounds date back to the 1800s, only relatively recently has there been general recognition of the many roles organostannanes have in synthesis. For example, organostannanes find applications in the free radical based generation of C-H and C-C bonds. Transmetalations also provide a range of transition metal catalyzed reactions. Much of this chemistry has been discussed by Lipshutz and coworkers.<sup>42,61</sup> Most organostannanes are relatively stable liquids or solids, which are easily handled in air and are largely insensitive to moisture. The toxicity of organostannanes has been extensively investigated, and as a rule these compounds should be regarded as hazardous materials.<sup>62</sup> The role of organostannanes that will be discussed in this section will of course be transmetalation to generate organocopper species.

Alkenylstannanes<sup>61,63</sup> as well as other classes such as  $\alpha$ -heteroatom-substituted alkyltributylstannanes<sup>64</sup> and more importantly, allylstannanes<sup>65</sup> also undergo these Sn-Cu transmetalations. Michael additions and other reactions typical of organocopper species can also be performed by Sn/Cu exchange.<sup>42</sup> Unlike many of the examples in previous sections, intramolecular reactions may be performed when tin is used as the organometallic precursor

(Scheme 20). This is a true testament to the mild, functional-group-tolerant nature of tin to copper methodology.<sup>66</sup>

**Scheme 20. Copper-promoted intramolecular conjugate addition from organostannanes<sup>66</sup>**



What remains absent is a transformation involving transmetalation with organotin and catalytic quantities of copper to perform conjugate addition reactions. Perhaps the reason behind this absence is the toxicity associated with organotin compounds, preventing the emergence of other methodology.

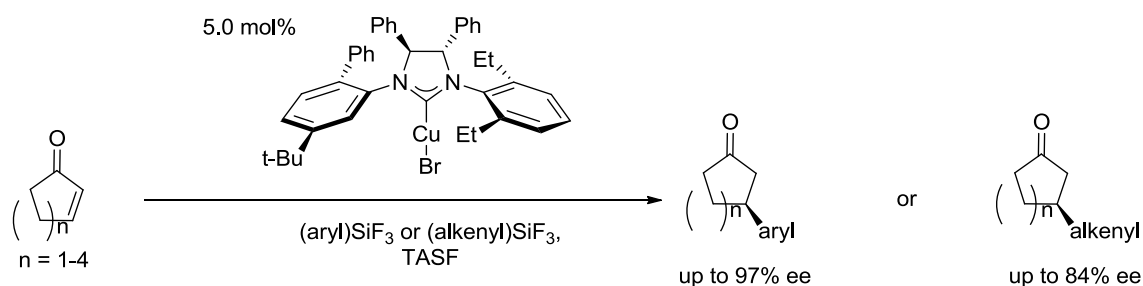
### 1.3.5 Transmetalation of organosilicon compounds

In contrast to other potential transmetalation partners, organosilanes are the attractive nucleophiles. Transmetalation with organosilanes has been greatly examined with respect to palladium<sup>67-71</sup> catalysis but very few reports exist for copper. The intermediacy of organocopper species has been inferred in reactions of highly strained silanes<sup>72</sup> and of those activated by intramolecular alkoxides.<sup>72-74</sup> A few reports demonstrating copper catalysts for organosilane dimerization,<sup>75</sup> for coupling of alkynylsilanes,<sup>76</sup> or for nucleophilic addition of organosilanes have appeared,<sup>77</sup> primarily with more easily transferable allylsilanes.<sup>78,79</sup> Noteworthy examples of

direct transmetalation have been observed and characterized with simple sp<sup>2</sup> and activated sp<sup>3</sup> organosilanes in this lab,<sup>80</sup> but will not be discussed until Chapter 4.

Most recently, Hoveyda and coworkers describe enantioselective conjugated addition to cyclic enones employing organo(trifluoro)silanes as nucleophiles in the presence of a fluoride additive (Scheme 21).<sup>81</sup> In the Hoveyda work, excellent yields and enantioselectivities are achieved. Again, there is little benefit in the way copper species bearing significant molecular complexity are generated due to the harsh nature in which organo(trifluoro)silanes are synthesized.

**Scheme 21. Enantioselective copper-catalyzed conjugate addition of organo(trifluoro)silanes to cyclic enones. Figure adapted from reference 79.**





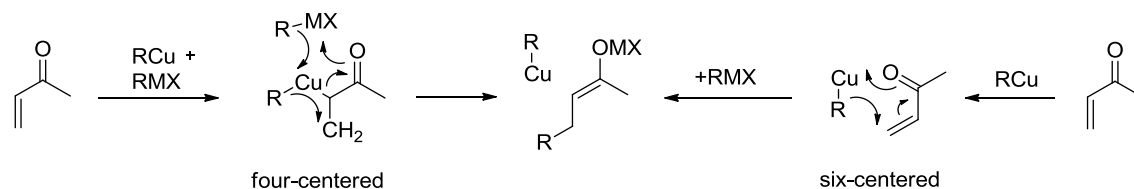
## 1.4 Mechanistic aspects of nucleophilic organocopper reagents

### 1.4.1 Stoichiometric conjugate addition

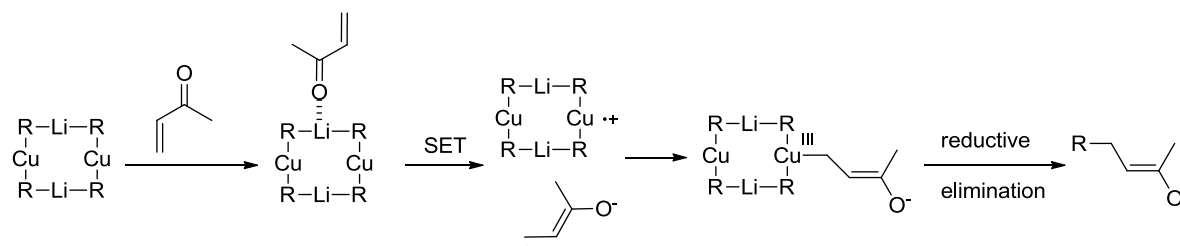
The organocopper reagents discussed in previous sections have mostly been in the form of nucleophilic organocopper(I) reagents, which are used either as stoichiometric reagents or as catalytic species generated in situ from a small amount of a copper(I) complex and a large amount of another organometallic reagent. The nucleophilic organocopper(I) reagents are commonly described as simple organocopper species,  $\text{RCu}(\text{ligand})$  and  $\text{R}_2\text{Cu}^-$ , or metal organocuprates such as  $\text{R}_n\text{Cu}(\text{X})\text{M}_m$ , where R, X, and M stand for a carbanion, a nontransferable anion, and a main-group metal cation, respectively. Such organocuprates serve as uniquely effective synthetic reagents for delivery of an organic nucleophile to electrophilic substrates. The chemistry of nucleophilic organocopper reagents has been reviewed many times with emphasis on synthetic utilities since the early 1970s.<sup>82</sup> Comprehensive information on the structure<sup>83</sup> and the electronic states of stable copper complexes, reactive intermediates, and transition states<sup>84</sup> of the reactions only became available more than 20 years later.<sup>85</sup>

The conjugate addition reaction of organocuprates to enones and related  $\alpha,\beta$ -unsaturated carbonyl compounds is undoubtedly the most versatile organocopper reaction and among the most useful C-C bond-forming reactions in organic synthesis. The mechanism of this reaction, among many organocuprate reactions, has been most extensively studied. A review in Organic Reactions published in 1992 listed three mechanistic possibilities of conjugate addition of a cuprate to an  $\alpha,\beta$ -unsaturated ketone,<sup>86</sup> namely, single-electron transfer, carbocupration, and nucleophilic copper mechanisms. Proposed mechanisms such as four-centered mechanisms (Scheme 22),<sup>87-89</sup> six-centered mechanisms (Scheme 22),<sup>90,91</sup> and now single-electron transfer theorems (Scheme 23)<sup>92,93</sup> are considered obsolete. After extensive experimental studies in the past 20 years supported by the theoretical analysis, it is now accepted that the nucleophilic copper mechanism is operating in a majority of the reactions.<sup>94</sup>

### Scheme 22. Four-centered and six-centered addition mechanisms

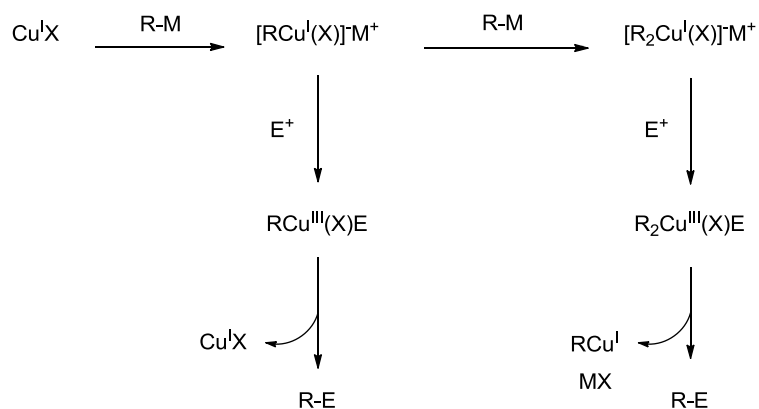


### Scheme 23. Single-electron transfer theorem



Regardless of stoichiometric or catalytic processes, the reactions have three elementary steps in common (Scheme 24), that is, transmetalation between a copper(I) salt and a main-group organometallic reagent to give either a mono- or di-organocuprate(I); oxidative addition to an organocopper(III) intermediate; and reductive elimination of the copper(III) intermediate to furnish a product and a copper(I) species. In a catalytic reaction, the last species takes part in the next catalytic step.<sup>94</sup> Thus, the transmetalation and the Cu(I)/Cu(III) redox sequence are common key processes in both stoichiometric and catalytic processes.

**Scheme 24. General mechanism of organocopper(I)-mediated C-C bond formation**

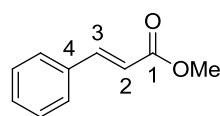


Though the single-electron transfer theorem is mostly no longer accepted, the suggestion that an important reactive intermediate is a Cu(III) species has survived the test of time.<sup>95</sup> Detailed structures of the intermediates were unknown for a long time. Support in this area came by subsequent NMR studies<sup>95-100</sup> and support from theoretical investigations.<sup>101-105</sup> The formation of the key carbon-carbon bond in these reactions has been proposed to be mediated by a Cu(III) intermediate formed by two-electron, inner sphere electron transfer.<sup>84</sup> The Gilman type cuprates ( $\text{Me}_2\text{CuLi}$ ) have become a generally accepted model for mechanistic and structural studies on copper-mediated reactions.

In conjugate addition reactions of organocuprates to Michael acceptors,  $\pi$ -complexes between cuprates and Michael acceptors were proposed theoretically<sup>106</sup> as first reaction intermediates and were later confirmed experimentally.<sup>98</sup> NMR has become the method of choice for the structure elucidation of these reaction intermediates because the  $\pi$ -bond carbons are expected to experience the highest chemical shift variations and can be used as sensors for the formation of  $\pi$ -intermediates. In one of the first literature-available NMR studies of organocuprate intermediates,<sup>107</sup> an organocuprate  $\pi$ -complex was stabilized using low-

temperature NMR in combination with methyl cinnamate as a relatively unreactive Michael acceptor. In the  $^{13}\text{C}$  spectra of methyl cinnamate and its organocuprate  $\pi$ -complex, upfield shifts of the  $\pi$ -bond carbons of  $\Delta\delta = -67.2$  ppm and  $-82.6$  ppm were detected (Table 1). In addition, a small downfield shift of the carbonyl carbon indicates lithium coordination at the carbonyl oxygen. Later on, via further studies of organocuprate  $\pi$ -complexes, these characteristic  $^{13}\text{C}$  chemical shift differences were detected and used as evidence for  $\pi$ -complexation.

**Table 1. Copper(I) organocuprate  $\pi$ -complex  $^{13}\text{C}$  NMR chemical shifts**

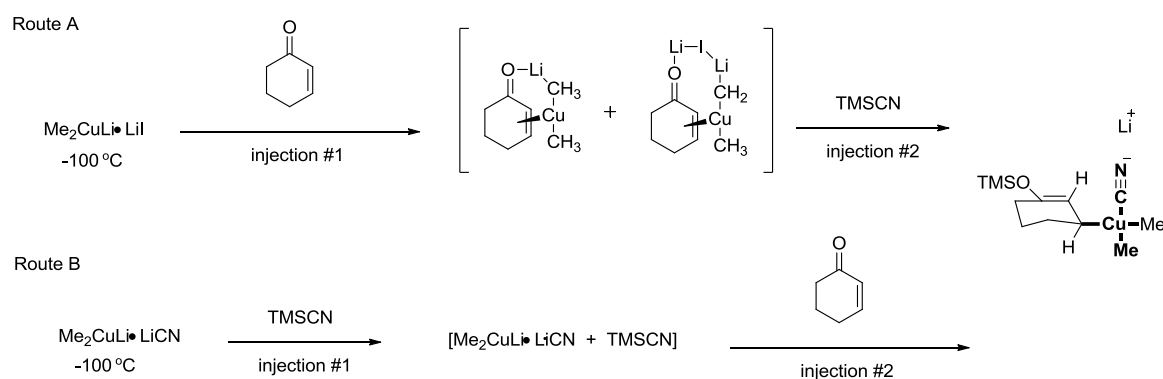


carbon number	C1	C2	C3	C4
methyl cinnamate	166.9 ppm	117.7 ppm	144.9 ppm	134.5 ppm
$\pi$ -complex with Gilman cuprate	173.9 ppm	52.0 ppm	61.8 ppm	143.4 ppm

Bertz and Ogle describe the observation of  $\pi$ -complexes from prototypical Gilman reagents with unhindered enones<sup>108</sup> and later on the first experimental observation of a Cu(III) intermediate in a conjugate addition reaction by rapid injection NMR (RI-NMR) using THF as a solvent.<sup>98,109</sup> RI- NMR is a useful technique which reduces the dead time before the NMR scan to a minimum and allows 1D NMR spectra within the first seconds of a reaction.<sup>110,111</sup> After the very first scan, the starting time for the second experiment is limited by the relaxation properties of the sample and typical repetition times range from 1-2s. Since the experiment can be carried out at  $-100\text{ }^{\circ}\text{C}$ , this technique allowed the preparation of the  $\pi$ -complex without enolate formation. They identified different  $\pi$ -complexes of  $\text{Me}_2\text{CuLi}\cdot\text{LiI}$  and  $\text{Me}_2\text{CuLi}\cdot\text{LiCN}$  with 2-cyclohexenone.<sup>96</sup>

As mentioned before, it is now established that the organocopper(III) complex is an important intermediate that is formed by oxidative addition of an electrophilic substrate to an organocuprate(I). Bertz and Ogle detected a Cu(III) intermediate of a 1,4-addition reaction with RI-NMR and demonstrated the use of TMSCN as a stabilizing agent for the Cu(III) enolate species.<sup>98</sup> The intermediate Cu(III) was trapped by the formation of a stable silyl enol ether (Scheme 25). With a double application of the RI-NMR technique, it was even possible to show experimentally that neither the kind of starting cuprate nor the injection sequence influences the formation of the Cu(III) sigma-complex. Route A first allows detection of  $\pi$ -complexes, whereas the further injection of TMSCN leads to the formation of the Cu(III) sigma-complex. In route B, the injection sequence starts with TMSCN and the identical Cu(III)  $\sigma$ -complex is observed after addition of the enone.

**Scheme 25. Copper(III)  $\sigma$ -complex from 1,4-addition to 2-cyclohexenone. Figure adapted from reference 96.**



Theoretical studies demonstrated that most copper(III) species are kinetically very unstable and undergo reductive elimination without an energy barrier, but, as seen in the work of Bertz and Ogle and others,<sup>84,112</sup> copper (III) can be stabilized by a donor ligand added to form a stable square-planar complex.

### 1.4.2 Catalytic conjugate addition

Because of the high reactivity of organolithium reagents, which causes direct coupling with the electrophile in the reaction mixture, organolithium reagents cannot be used for catalytic reactions, with rare exceptions.<sup>113</sup> On the other hand, mildly nucleophilic organometallic reagents such as organozinc reagents usually, if not always, give rise to monoorganocuprates regardless of stoichiometric or catalytic conditions. The nucleophilicity of Grignard reagents being intermediary, they can generate either monoorganocuprates or diorganocuprates as major species depending on the reaction.<sup>114</sup> At present, a multitude of copper/ligand combinations are accessible in organic synthesis,<sup>113</sup> yet there is only scant information available about Cu(I)-catalyzed reaction mechanisms. Nonetheless, it is widely believed that the stoichiometric and catalytic reactions share the same mechanistic principles. Therefore, catalytic cycles consisting of transmetalation, oxidative addition, and reductive elimination are considered to be plausible for copper-catalyzed conjugate addition.<sup>115</sup> While little consensus has been reached on the fine details of the mechanism, it is generally believed that the reactions operate on the Cu(I)/Cu(III) catalytic cycle even when a copper(II) salt is used as a precatalyst.

There are proposed mechanisms that suggest that some NHC ligated systems remain copper(I) throughout the catalytic cycle.<sup>60</sup> Rather than proceed through oxidative addition, the functionalized organocopper species executes a migratory insertion on the  $\alpha,\beta$ -unsaturated carbonyl compound.

## 1.5 Conclusion

Organometallic chemistry continues to be a growing field due to the outstanding transformations that transition metals provide. Organocopper chemistry will continue to lend itself as a significant set of tools to tackle synthetic obstacles. There are three principal reactions

where the organocopper species are more effective than their precursor organolithium and organomagnesium reagents: conjugated addition to an electron deficient olefin, simple addition reactions to alkyl halides, tosylates, and epoxides, and carbometalation across alkynes. While these reactions have contributed to the success of many target-oriented syntheses, large gaps in the methodology remain due to the lack functional group tolerance, toxicity of byproducts, and a lack of mild yet reactive precursors.

Transmetalations of various organometallic species with copper have been found to produce highly useful organocopper reagents of great synthetic interest. Many different organometallic precursors have proved valuable, depending of the functionality present in the copper reagent. The scope of organocopper chemistry has been greatly enhanced by these new transmetalation reactions and these reagents have many applications in organic synthesis.

As summarized in the preceding sections, the importance of  $[\text{Cu}]^{\text{III}}$  species is now fully recognized. This necessitates a better understanding of the structure and dynamics of organocopper compounds, in order to enable faster reaction optimization processes and, to some extent, a rational control of the reactivity.

Copper-mediated reactions play important roles in the synthesis of natural and unnatural products. To date natural product synthesis using organocopper reagents have been accomplished, and will undoubtedly be continued to be used in the future as well.

## 1.6 References

- (1) Peng, Y.; Li, W. D. Z. *Eur. J. Org. Chem.* **2010**, 6703.
- (2) Seyferth, D. *Organometallics* **2009**, 28, 2.
- (3) Lan, Y.; Deng, L. J.; Liu, J.; Wang, C.; Wiest, O.; Yang, Z.; Wu, Y. D. *J. Org. Chem.* **2009**, 74, 5049.
- (4) Devasagayaraj, A.; Knochel, P. *Tetrahedron Lett.* **1995**, 36, 8411.
- (5) Lipshutz, B. H., Sengupta, S. *Org. Reactions* **1992**, 41, 135.
- (6) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, 63, 2308.
- (7) Normant, J. F. *Organocopper Reagents - A Practical Approach, Chapter 11*, Oxford University Press, New York, 237.
- (8) Alexakis, A.; Jachiet, D.; Normant, J. F. *Tetrahedron* **1986**, 42, 5607.
- (9) Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, 89, 3911.
- (10) Buckton, G. *Ann.* **1859**, 109, 225.
- (11) Reich, R. C. R. *Hebd. Seances Acad. Sci.* **1923**, 177, 322.
- (12) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, 17, 1630.
- (13) Krause, N.; Gerold, A. *Angew. Chem. Int. Ed.* **1997**, 36, 187.
- (14) House, H. O.; Respass, W. L.; Whiteside, G. M. *J. Org. Chem.* **1966**, 31, 3128.
- (15) Miyashita, A.; Yamamoto, T.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1977**, 50, 1109.
- (16) Rieke, R. D.; Klein, W. R.; Wu, T. C. *Journal of Organic Chemistry* **1993**, 58, 2492.
- (17) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343.
- (18) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, 285, 437.
- (19) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, 95, 7788.
- (20) Hjelmgaard, T.; Tanner, D. *Org. Biomol. Chem.* **2006**, 4, 1796.
- (21) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, 53, 2390.
- (22) Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Letters* **1987**, 28, 2053.



- (23) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* **2008**, *108*, 2796.
- (24) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.
- (25) Ireland, R. E.; Vanasse, B.; Wipf, P. *Abstracts of Papers of the American Chemical Society* **1990**, *199*, 7.
- (26) Ireland, R. E.; Wipf, P.; Roper, T. D. *J. Org. Chem.* **1990**, *55*, 2284.
- (27) den Hartog, T.; Harutyunyan, S. R.; Font, D.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 398.
- (28) Ireland, R. E.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425.
- (29) Alexakis, A.; Cahiez, G.; Normant, J. F. *Tetrahedron Lett.* **1978**, 2027.
- (30) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1980**, *21*, 1433.
- (31) Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, N. K. *Tetrahedron Lett.* **1983**, *24*, 4359.
- (32) Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 2327.
- (33) Rappoport, Z. *The Chemistry of Organocopper Compounds Part 1* **2009**.
- (34) Selim, K. B.; Nakanishi, H.; Matsumoto, Y.; Yamamoto, Y.; Yamada, K.; Tomioka, K. *J. Org. Chem.* **2011**, *76*, 1398.
- (35) Delp, S. A.; Munro-Leighton, C.; Goj, L. A.; Blue, E. D.; Gunnoe, T. B.; Petersen, J. L.; Cundari, T. *Abstracts of Papers of the American Chemical Society* **2006**, 232.
- (36) Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416.
- (37) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789.
- (38) Knochel, P. *Synlett* **1995**, 393.
- (39) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.
- (40) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440.
- (41) Lipshutz, B. H.; Kato, K. *Tetrahedron Lett.* **1991**, *32*, 5647.
- (42) Lipshutz, B. H.; Lee, J. I. *Tetrahedron Lett.* **1991**, *32*, 7211.
- (43) Wipf, P.; Smitrovich, J. H. *J. Org. Chem.* **1991**, *56*, 6494.
- (44) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
- (45) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 1097.
- (46) Kacprzynski, M. A.; Kazane, S. A.; May, T. L.; Hoveyda, A. H. *Org. Lett.* **2007**, *9*, 3187.

- (47) Gendrineau, T.; Genet, J. P.; Darses, S. *Org. Lett.* **2009**, *11*, 3486.
- (48) Iannazzo, L.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C.; Gandon, V. *Eur. J. Org. Chem.* **2011**, 3283.
- (49) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 3795.
- (50) Asano, S.; Kamioka, S.; Isobe, Y. *Tetrahedron* **2012**, *68*, 272.
- (51) Chen, C.; Qiu, H. Y.; Chen, W. Z. *J. Organomet. Chem.* **2012**, 696, 4166.
- (52) Dodonova, J.; Skardziute, L.; Kazlauskas, K.; Jursenas, S.; Tumkevicius, S. *Tetrahedron* **2012**, *68*, 329.
- (53) Hadebe, S. W.; Sithebe, S.; Robinson, R. S. *Tetrahedron* **2011**, *67*, 4277.
- (54) Taylor, B. L. H.; Jarvo, E. R. *J. Org. Chem.* **2011**, *76*, 7573.
- (55) Miyaoura, N.; Sasaki, N.; Itoh, M.; Suzuki, A. *Tetrahedron Lett.* **1977**, 173.
- (56) Yatagai, H. *J. Org. Chem.* **1980**, *45*, 1640.
- (57) Brown, H. C.; Molander, G. A. *J. Org. Chem.* **1981**, *46*, 645.
- (58) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.
- (59) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 8656.
- (60) Takatsu, K.; Shintani, R.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 5548.
- (61) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.
- (62) Nath, M. *Appl. Organomet. Chem.* **2008**, *22*, 598.
- (63) Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609.
- (64) Falck, J. R.; Bhatt, R. K.; Ye, J. H. *J. Am. Chem. Soc.* **1995**, *117*, 5973.
- (65) Lipshutz, B. H.; Crow, R.; Dimock, S. H.; Ellsworth, E. L.; Smith, R. A. J.; Behling, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 4063.
- (66) Piers, E.; McEachern, E. J.; Burns, P. A. *J. Org. Chem.* **1995**, *60*, 2322.
- (67) Bi, L.; Georg, G. I. *Org. Lett.* **2011**, *13*, 5413.
- (68) Blakemore, D. C.; Marples, L. A. *Tetrahedron Lett.* **2011**, *52*, 4192.
- (69) Marcuccio, S. M.; Epa, R.; Moslmani, M.; Hughes, A. B. *Tetrahedron Lett.* **2011**, *52*, 7178.
- (70) Molander, G. A.; Iannazzo, L. *J. Org. Chem.* **2011**, *76*, 9182.
- (71) Lee, J. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616.

- (72) Franz, A. K.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 949.
- (73) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811.
- (74) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450.
- (75) Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 985.
- (76) Lermontov, S. A.; Rakov, I. M.; Zefirov, N. S.; Stang, P. J. *Tetrahedron Lett.* **1996**, *37*, 4051.
- (77) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138.
- (78) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536.
- (79) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
- (80) Herron, J. R.; Ball, Z. T. *J. Am. Chem. Soc.* **2008**, *130*, 16486.
- (81) Lee, K.-S.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455.
- (82) Normant, J. F. *Synthesis-International Journal of Methods in Synthetic Organic Chemistry* **1972**, 63.
- (83) Power, P. P. *Prog. Inorg. Chem.* **1991**, *39*, 75.
- (84) Nakamura, E.; Mori, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3750.
- (85) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393.
- (86) Lipshutz B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
- (87) Munchpetersen, J.; Andersen, V. K.; Jart, A.; Jorgensen, P. M.; Bretting, C.; Refn, S. *Acta Chem. Scand.* **1961**, *15*, 277.
- (88) Ryu, I.; Nakahira, H.; Ikebe, M.; Sonoda, N.; Yamato, S.; Komatsu, M. *J. Am. Chem. Soc.* **2000**, *122*, 1219.
- (89) Berlan, J.; Koosha, K.; Battioni, J. P. *Bulletin De La Societe Chimique De France Partie Ii-Chimie Moleculaire Organique Et Biologique* **1978**, 575.
- (90) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 4635.
- (91) Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1989**, *111*, 6524.
- (92) House, H. O.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 5495.
- (93) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

- (94) Yoshikai, N.; Iida, R.; Nakamura, E. *Adv. Synth. Catal.* **2008**, 350, 1063.
- (95) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, 26, 6015.
- (96) Bertz, S. H.; Carlin, C. M.; Deadwyler, D. A.; Murphy, M. D.; Ogle, C. A.; Seagle, P. H. *J. Am. Chem. Soc.* **2002**, 124, 13650.
- (97) Bertz, S. H.; Cope, S.; Dorton, D.; Murphy, M.; Ogle, C. A. *Angew. Chem. Int. Ed.* **2007**, 46, 7082.
- (98) Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, 129, 7208.
- (99) Bertz, S. H.; Ogle, C. A.; Rastogi, A. *J. Am. Chem. Soc.* **2005**, 127, 1372.
- (100) Bertz, S. H.; Ogle, C. A.; Snyder, J. P. *Abstracts of Papers of the American Chemical Society* **2006**, 232.
- (101) Mori, S.; Nakamura, E. *Tetrahedron Lett.* **1999**, 40, 5319.
- (102) Mori, S.; Nakamura, E. *Chem. Eur. J.* **1999**, 5, 1534.
- (103) Mori, S.; Nakamura, E. *Journal of Molecular Structure-Theochem* **1999**, 461, 167.
- (104) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, 119, 4900.
- (105) Nakamura, E.; Mori, S.; Nakamura, M.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, 119, 4887.
- (106) Nakamura, E.; Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2004**, 77, 1.
- (107) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, 282, 133.
- (108) Murphy, M. D.; Seagle, H. P.; Bertz, S. H.; Carlin, C. M.; Ogle, C. A. *Abstracts of Papers of the American Chemical Society* **2003**, 225, U407.
- (109) Bartholomew, E. R.; Bertz, S. H.; Cope, S.; Dorton, D. C.; Murphy, M.; Ogle, C. A. *Chem. Commun.* **2008**, 1176.
- (110) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, 107, 1805.
- (111) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *J. Am. Chem. Soc.* **1985**, 107, 1810.
- (112) Dorigo, A. E.; Wanner, J.; Schleyer, P. V. *Angew. Chem. Int. Ed.* **1995**, 34, 476.
- (113) Perez, M.; Fananas-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Nat. Chem.* **2011**, 3, 377.
- (114) Backvall, J. E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, 112, 6615.
- (115) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, 108, 2824.



# Chapter 2

## **Organosilicon reagents as nucleophiles in transition-metal catalyzed carbon-carbon bond forming reactions**

### **2.1 Introduction**

The use of silicon-derived compounds as alternative nucleophilic reagents for metal-catalyzed carbon-carbon bond formation has attracted attention due to their low cost, easy availability, and environmentally benign nature. Many organosilanes remain unaffected in the presence of harsh reaction conditions that may be encountered throughout the course of a total synthesis; hence their indispensable role as protecting groups. However, organosilanes are exquisitely sensitive to fluoride in comparison to most organic functional groups. These aforementioned properties assisted the development of mild coupling reactions with a range of electrophiles in the presence of sensitive functionality of all kinds. Following the emergence of these methodologies, organosilicon reagents have been employed as nucleophiles in the synthesis of a wide variety of natural products and biologically active compounds.<sup>1-5</sup>

Various organosilicon reagents are now available owing to the growth of the silicon industry. Many valuable vinylsilane substrates are easily obtained through the straightforward and atom economical route of hydrosilylation.<sup>6</sup> In addition, the configuration of a silyl-substituted

carbon is stable. Thus, optically active organosilicon compounds are available via asymmetric reactions.<sup>7</sup>

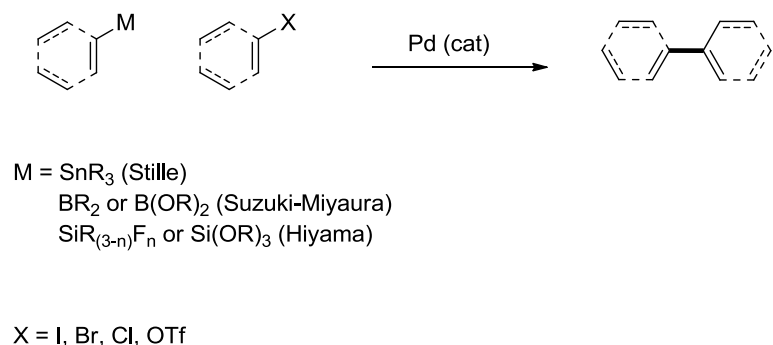
Organosilanes have broad application in palladium-catalyzed cross-coupling reactions ensuring their status as important intermediates in synthesis. This discussion will begin with one of the most notable achievements in this field, palladium-catalyzed Hiyama cross-coupling. Following this topic, brief discussions of transformations involving copper and rhodium will be presented. These methodologies are significant but studies are scarce in the literature.

## 2.2 Hiyama cross-coupling

Palladium-catalyzed cross-coupling reactions of organometallic species with various electrophiles are of vital importance in organic chemistry.<sup>8</sup> The protocols employing palladium-catalyzed transformations toward the synthesis of the desired cross-coupled products appears to be generally superior to related methods involving nickel, copper, iron, or cobalt catalysts in scope and in stereo-, regio-, and chemoselectivity.<sup>8</sup> Although organomagnesium, -zinc, -tin, and -aluminum reagents have been successfully used for the palladium-catalyzed cross-coupling reaction with organic halides, these reaction conditions are often considered to be less desirable due to the lack of functional-group tolerance.<sup>8</sup> Among the palladium-catalyzed reactions, (Scheme 1) Stille cross-coupling (organostannane) and Suzuki cross-coupling (organoboron), occupy a special place as indispensable methods to prepare cross-coupled products.<sup>8</sup> These methodologies are significantly milder and have been used in many important total syntheses of natural products in key late stage carbon-carbon bond formation steps.<sup>1</sup> However, certain drawbacks to these methods, including the toxicity and high molecular weight associated with tin

and the limited stability and coupling efficiency of organoboranes, constitute important limitations.<sup>9,10</sup>

### Scheme 1. Palladium-catalyzed cross-coupling reactions



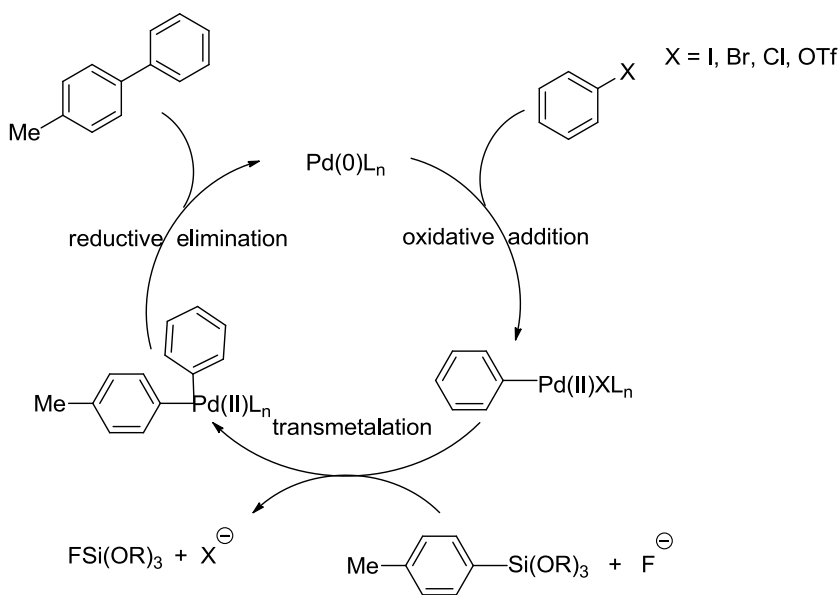
An additional widely used method employs organosilicon compounds as nucleophilic coupling partners (Scheme 1). The pioneering work of Hiyama and coworkers has demonstrated that organosilanes, when suitably functionalized and in the presence of a nucleophilic activator, can undergo similar cross-coupling reactions with palladium catalysis.<sup>11,12</sup> This discovery stimulated many investigations which revealed the utility of chloro- and fluorosilanes,<sup>13</sup> alkoxy-silanes,<sup>14-19</sup> siletanes,<sup>20</sup> silanols,<sup>21</sup> and silyl ethers<sup>9</sup> as versatile cross-coupling partners with a variety of electrophiles in excellent yields.



### 2.2.1 Mechanistic aspects of Hiyama cross-coupling

The catalytic cycle of the Hiyama reaction is generally believed to proceed in the method shown below (Scheme 2). Oxidative addition of an organohalide to the Pd(0) complex results in the formation of a R-Pd(II)-X species. The reaction also involves fluoride attack of an organosilane to form an anionic species that was later proved to be a pentacoordinated silicate.<sup>16</sup> Generation of a silicate species was shown to be essential for smooth transmetalation between the R-Pd(II)-X complex and the organosilane.<sup>13</sup> Transmetalation results in a (R)(R')Pd(II) species that undergoes reductive elimination to produce the cross-coupled product and regenerate an active Pd(0) complex.

**Scheme 2. General catalytic cycle of Hiyama cross-coupling**

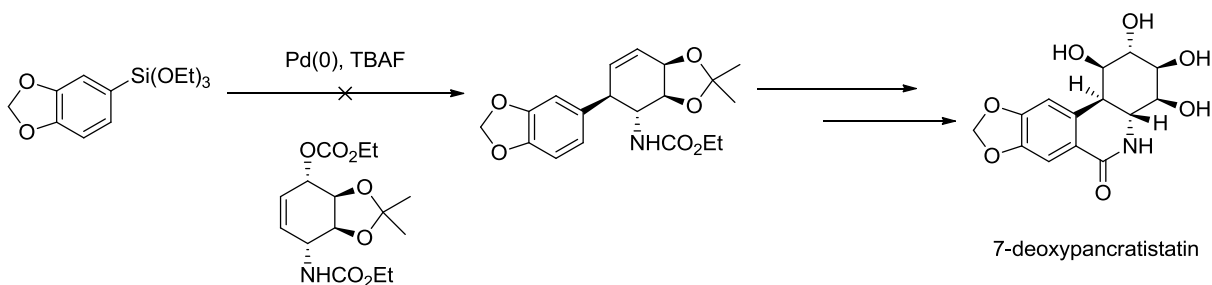


In many reports, authors claim that transmetalation is the turnover-limiting step.<sup>4,22-25</sup>

One mechanistic study of the palladium-catalyzed cross-coupling between arylsiloxanes and allyl

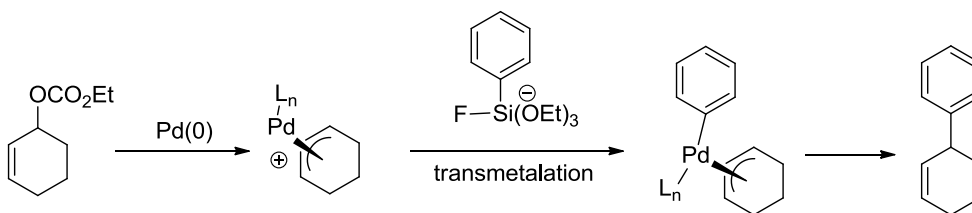
carbonates from DeShong and coworkers was initiated as a result from failure to perform a cross-coupling reaction under Hiyama conditions for the synthesis of 7-deoxypancratistatin (Scheme 3).<sup>22</sup>

**Scheme 3. Unsuccessful cross-coupling attempt for the synthesis of 7-deoxypancratistatin<sup>22</sup>**



Initially, DeShong and coworkers assumed that the steric bulk of the allyl carbonate was responsible for the absence of coupled product. This hypothesis was quickly dismissed after succeeding to couple the sterically demanding allyl carbonate with a variety of other nucleophilic coupling partners, revealing that either transmetalation or reductive elimination was responsible for the failure of the reaction.<sup>26</sup>

**Scheme 4. Cross-coupling of cyclohexenyl carbonate with phenyltriethoxysilane<sup>20</sup>**

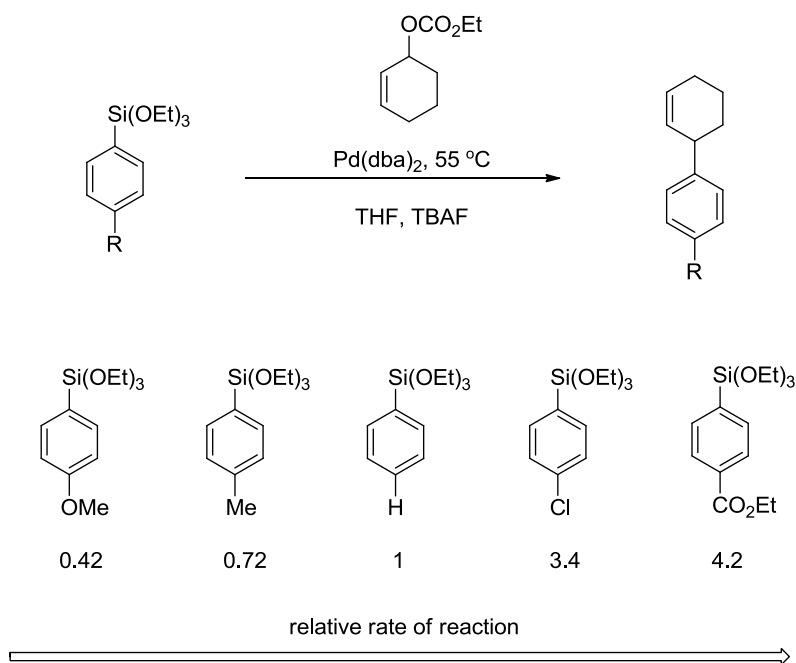


In view of Hiyama's findings that generation of a pentacoordinated silicon is a prerequisite to successful transmetalation,<sup>11,12</sup> the reaction of fluoride anion (from TBAF) with the phenyltriethoxysilane was studied by <sup>19</sup>F NMR. DeShong and coworkers concluded that silicate formation was not rate-determining. The siloxane derivative reacted with fluoride ion to provide a hypercoordinate silicate much more rapidly than the coupling reaction of cyclohexenyl carbonate (a known substrate to undergo facile cross-coupling) occurred (Scheme 4).

Following these results, a series of para-substituted-arylsiloxane derivatives (R = OMe, Me, Cl, CO<sub>2</sub>Et) were compared with phenyltriethoxysilane in the Pd-catalyzed coupling with cyclohexenyl carbonate to construct a Hammett plot (Figure 1). The results revealed that the relative rate of transmetalation was enhanced by electron-withdrawing groups ( $\rho = 1.4$ ).<sup>22</sup> This outcome indicates that either transmetalation or reductive elimination is the turnover-limiting step. This effect would not be observed if the formation of the  $\pi$ -allyl intermediate was rate-determining.

**Figure 1. Summary of relative rates of coupling reaction with siloxane derivatives.**

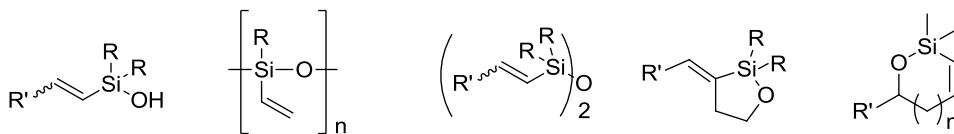
Figure adapted from reference 20.



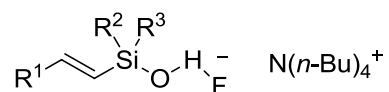
DeShong relies on a report by Kurosawa and coworkers<sup>27,28</sup> to propose that transmetalation rather than reductive elimination is the turnover-limiting step. The Kurosawa report presents a measured rate of reductive elimination of an allyl-aryl palladium complex (prepared from another methodology) that thermally decomposes quickly. This evidence, while circumstantial, suggests that the rate of reductive elimination would be much faster than the rate of coupling observed in the DeShong report, pointing to transmetalation as the turnover-limiting step. This hypothesis is also supported by the absence of coupled product in the 7-deoxypancratistatin synthesis (Scheme 3), making it reasonable to assume that transmetalation had not occurred.

Under the assumption that transmetalation is the turnover-limiting step in Hiyama-type cross-coupling reactions, many research groups have developed methods that focus on the design of new silicon subunits with enhanced reactivity in order to promote transmetalation (Figure 2).<sup>21</sup> The Hiyama, Denmark, and DeShong labs have been instrumental in the development of silanes that possess improved reactivity. Summaries of synthesis for new silicon substrates, implementation, and mechanistic details have been thoroughly reviewed.<sup>20,21</sup>

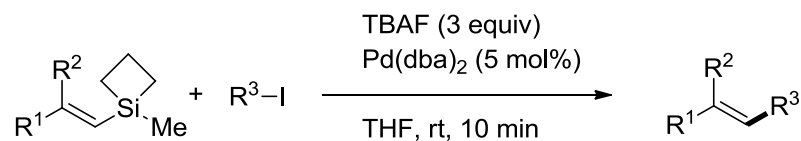
**Figure 2. Organosilane coupling partners**



Due to the high affinity of fluoride for silicon ( $\text{Si-F} = 135 \text{ kcal/mol}$ ),<sup>29</sup> the use of a fluoride ion source (TBAF, TBAT, TMAF, TASF, KF, or CsF) together with organosilane coupling partner provide the necessary pentacoordinate fluorosilicate intermediates for transmetalation. <sup>29</sup>Si NMR spectroscopic studies on the use of TBAF as a promoter for the palladium-catalyzed cross-coupling of several types of alkenylsilanes (alkenylsiletanes, alkenylsilyl halides, alkenylalkoxysilanes, alkenyldisiloxanes, and alkenylsilanols) provide that all of these precursors react via a common intermediate, hypothesized to be a hydrogen-bonded silanol-fluoride adduct (Figure 3).<sup>30</sup> Because of this mechanistic commonality, a wide range of organosilanes display similar reactivity yet provide a variety of precursor options.<sup>30-33</sup>

**Figure 3. Hydrogen-bonded silanol-fluoride adduct**

Alkenylsilacyclobutanes represent a special class of alkenyl(trialkyl)silanes that can undergo facile palladium-catalyzed cross-coupling with aryl and vinyl iodides (Scheme 5).<sup>21</sup> These reactions proceed rapidly in the presence of 3 equiv of TBAF and 5 mol % of Pd(dba)<sub>2</sub> in THF at ambient temperature. Alkenylsiletanes, which can be readily prepared from organometallic addition to 1-chloro-1-methylsilacyclobutane, originally were thought to undergo cross-coupling this rapidly due to the enhanced Lewis acidity of the silicon center from strain release during the formation of the pentacoordinate fluorosiliconate.<sup>21</sup> However, under the reaction conditions, the siletanes are observed to undergo a fast initial ring opening to form alkenyl(propyl)(methyl)-silanols, which are most likely the active species for the cross-coupling reaction.<sup>30</sup> Direct comparisons to alkenylsilanols, alkenylsilyl halides, and alkenylsilyl ethers reveal a similar reactivity, and corroborate the observation that these alkenylsilanes react via the same intermediate.<sup>30</sup>

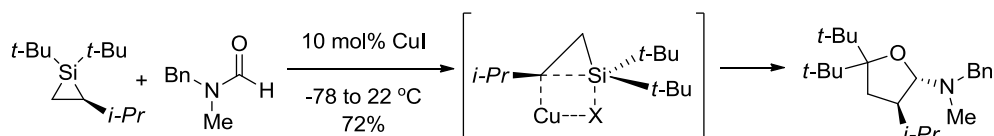
**Scheme 5. Alkenylsiletanes for facile palladium-catalyzed cross-coupling with organoiodides<sup>30</sup>**

## 2.3 Copper-catalyzed processes employing organosilanes as nucleophiles

Copper can catalytically promote a wide variety of useful transformations. Many of these reactions were presented in Chapter 1. In this section, Cu(I)F-catalyzed asymmetric carbon-carbon bond-forming reactions via the addition of organosilanes as nucleophiles to various electrophiles will be discussed.

While the transmetalation with organosilanes has been greatly examined with respect to palladium, very few reports exist for copper. The intermediacy of organocopper species has been inferred in reactions of highly strained silanes<sup>34</sup> and of those activated by intramolecular alkoxides.<sup>34-36</sup> Only a few reports for copper promoted nucleophilic addition of organosilanes have appeared.<sup>37-42</sup>

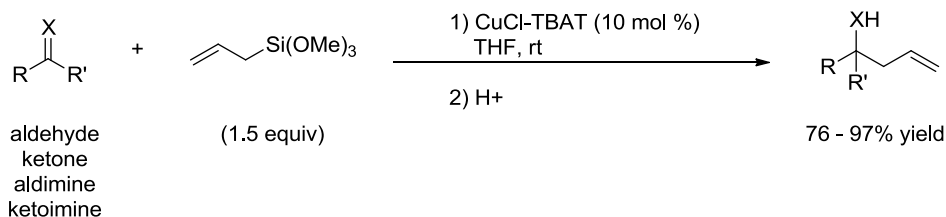
### Scheme 6. Reaction of silacyclopropanes with carbonyl compounds catalyzed by copper salts<sup>34</sup>



#### 2.3.1 Copper catalyzed allylation carbonyl compounds

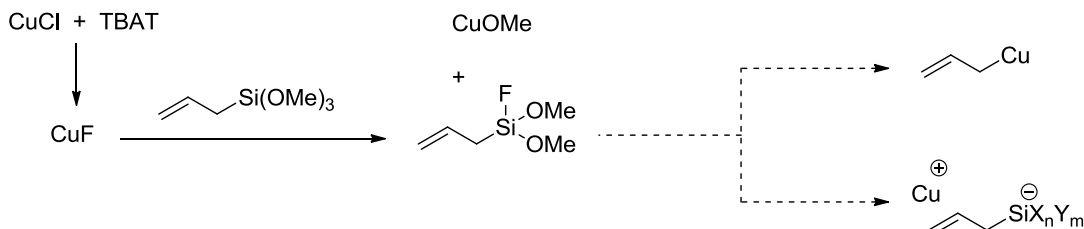
In 2002, Shibasaki and coworkers developed a general catalytic allylation using copper salts as catalyst, a fluoride source, and allyltrimethoxysilane as a nucleophile (Scheme 6).<sup>38</sup> This basic methodology for allylation covers substrates including aldehydes, ketones, aldimines, and ketimines. Simple extension of this method to a catalytic asymmetric allylation of ketones using chiral bisphosphines provided enantioselectivities up to 86%.

**Scheme 7. Copper-catalyzed allylation of carbonyl compounds with allyltrimethoxysilane<sup>38</sup>**



The reaction mechanism is ambiguous (Scheme 7). While, allylsilanes are known to perform allylations in the presence of Lewis acids, allyltrimethoxysilane is significantly less reactive.<sup>43</sup> Shibasaki efforts to gain mechanistic insights into the reaction were aided by the use of <sup>19</sup>F NMR. Using tetrabutylammonium difluorotriphenylsilicate (TBAT) as a soluble, anhydrous fluoride source and copper chloride afforded a new peak at -155.7 ppm (broad). Shibasaki assigns this peak to be copper(I) fluoride, however, it is well known that copper(I) fluoride is unstable toward disproportionation. This new peak is more likely the result of cuprate formation (F-Cu-Cl<sup>-</sup>, F-Cu-Si(R<sub>n</sub>X<sub>m-n</sub>), etc.). Regardless, addition of allyltrimethoxysilane causes this peak to disappear while a new peak at -129.0 ppm appears which is reasonably assigned as allylfluorodimethoxysilane. Further investigations indicate that the fluoride ion is important for initiation of reaction and plays an active role in the catalytic cycle. When CuO*t*Bu and allyltrimethoxysilane were mixed (1:1) in THF, <sup>1</sup>H and <sup>13</sup>C NMR did not indicate any interaction between these two species. Upon addition of (EtO)<sub>3</sub>SiF (1 equiv) to this mixture, however, two peaks (-149.1 ppm and -155.3 ppm [(EtO)<sub>3</sub>SiF]), appeared in the <sup>19</sup>F NMR spectrum, indicating Si-Si ligand exchange. It is necessary to mention that this ligand exchange did not occur in the absence of the copper alkoxide. While there is no conclusive evidence of silicon-copper transmetalation, the reaction does not proceed without copper and fluoride source.



**Scheme 8. Proposed reactive intermediates providing observed products<sup>38</sup>**

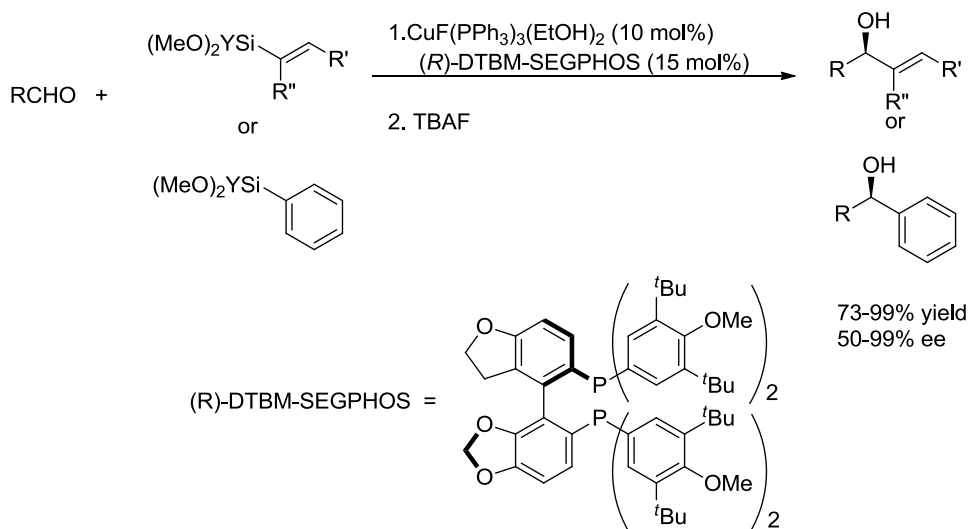
In 2004, Shibasaki introduced a new protocol for catalytic enantioselective allylations using allylboron reagents.<sup>44</sup> Identical enantioselectivities of the allylation products were obtained from boron and silane chemistry. Shibasaki suggests that an allyl copper intermediate is the likely nucleophile generated through transmetalation from silicon to copper and from boron to copper. There is little evidence supporting this claim. Boronates and silicates may be the active nucleophiles with copper acting as a chiral Lewis acid. While the mechanistic details are inconclusive, the Shibasaki reports are noteworthy examples of catalytic enantioselective allylation chemistry.<sup>38,43,45</sup>

### 2.3.2 Copper-catalyzed addition of vinyl- and arylsilanes to carbonyl compounds

While silicon to copper transmetalation has been reported, there were no examples of vinyl transfer for the purpose of nucleophilic addition to carbonyl compounds prior to a report by Shibasaki in 2005 (Scheme 8).<sup>37</sup> In this reaction, excellent enantioselectivity was observed for a

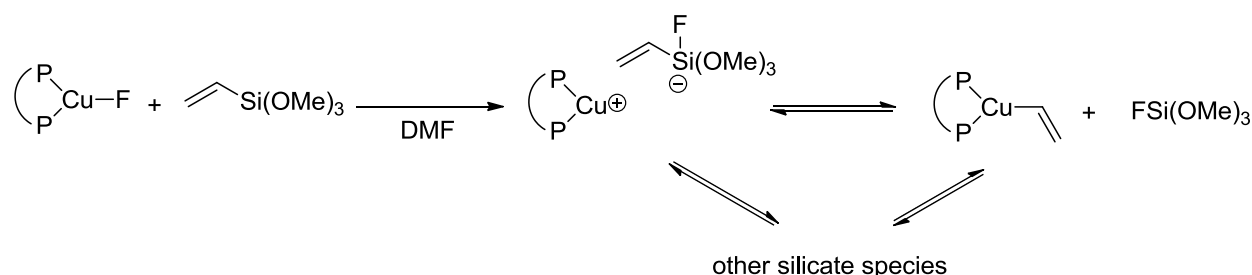
range of aldehydes, including aromatic,  $\alpha,\beta$ -unsaturated, and aliphatic aldehydes. Shibasaki and coworkers claim that this reaction proceeds through an active alkenyl copper nucleophile, generated by transmetalation of copper and silicon. In contrast to the allylation chemistry discussed in section 2.3.1, this claim is more convincing.

**Scheme 9. Copper-catalyzed 1,2-addition of alkenylsilanes to carbonyl compounds<sup>37</sup>**



Shibasaki and coworkers begin with a known ligand-stabilized copper(I)fluoride source,<sup>46</sup> eliminating some questions present in the allylation chemistry report (section 2.2.1). Also in support of their claim, the reaction with the (DTBM-SEGPHOS) copper(I) fluoride complex and vinyltrimethoxysilane afforded a  $^{19}F$  NMR peak at -147.0 ppm corresponding to  $(MeO)_3SiF$ . Surprisingly, no  $^1H$  and  $^{13}C$  NMR studies were presented for this mixture.<sup>37</sup> The vinylcopper species (Scheme 9) would be expected to give diagnostic chemical shifts.<sup>47</sup>

**Scheme 10. Proposed reactive intermediates providing observed products supported by  $^{19}\text{F}$  NMR experiments<sup>37</sup>**

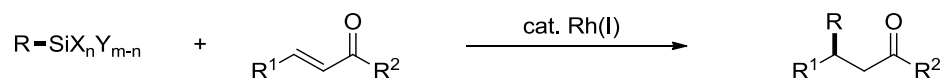


In stark contrast with Shibasaki's vinylboronate chemistry,<sup>44</sup> this system is compatible with linear aliphatic aldehydes and simple ketones. This methodology successfully delivers excellent yields and enantioselectivities for the assembly of chiral allylic alcohols using air- and moisture-stable alkenyl- and phenylsilanes as nucleophiles.

## 2.4 Rhodium-catalyzed 1,4-addition to $\alpha,\beta$ -unsaturated carbonyl compounds

Conjugate addition of organometallic reagents to  $\alpha,\beta$ -unsaturated carbonyl compounds is an important means for C–C bond formation in organic synthesis.<sup>48</sup> This reaction was once limited to organocopper chemistry (section 1.2) but is now possible with other transition metal catalysts.<sup>49–53</sup> In the presence of a rhodium catalyst,  $\alpha,\beta$ -unsaturated carbonyl compounds react with arylbismuth, organotin, aryllead, and organoboron to give the corresponding conjugate addition products.<sup>54–58</sup> This rhodium-catalyzed 1,4-addition methodology has been extended to include organosilanes (Scheme 10) as capable nucleophiles for a range of electron deficient olefins.<sup>59,60</sup>

**Scheme 11. Rhodium-catalyzed 1,4 addition of organosilanes to  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>59</sup>**

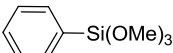

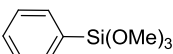

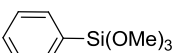

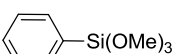
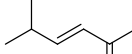
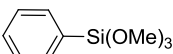
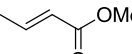
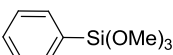
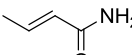
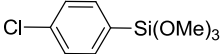

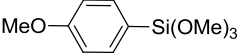

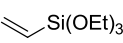

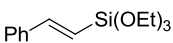

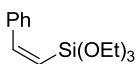



The method employing organosilanes has several advantages over other 1,4-addition reactions: (1) The organosilanes used in this methodology are stable to oxygen and moisture, permitting the reaction to run in protic media or even in an aqueous solution. (2) The organosilanes are much less reactive toward enones in the absence of a rhodium catalyst than the organometallic reagents so far used, such as organomagnesium or -lithium reagents, and no 1,2-addition to enones takes place in the presence or absence of the catalyst. (3) The reaction is catalyzed by transition-metal complexes often coordinated with phosphine ligands.<sup>60</sup> Since chiral phosphine ligands are the chiral auxiliaries most extensively studied for transition-metal-catalyzed asymmetric reactions, one can use the accumulated knowledge of the chiral phosphine ligands to select the appropriate ligand for the asymmetric reaction.

Inoue and coworkers reported a rhodium-catalyzed, highly enantioselective 1,4-addition of organosiloxanes to  $\alpha,\beta$ -unsaturated carbonyl compounds in 2002 (Table 1).<sup>60</sup> Good to excellent yields were observed for a range of silyl-nucleophiles and  $\alpha,\beta$ -unsaturated carbonyl compounds including  $\alpha,\beta$ -unsaturated esters (entry 5) and  $\alpha,\beta$ -unsaturated amides (entry 6). Even hindered enones (entry 4) were well tolerated. Both electron-rich (entry 8) and electron-poor

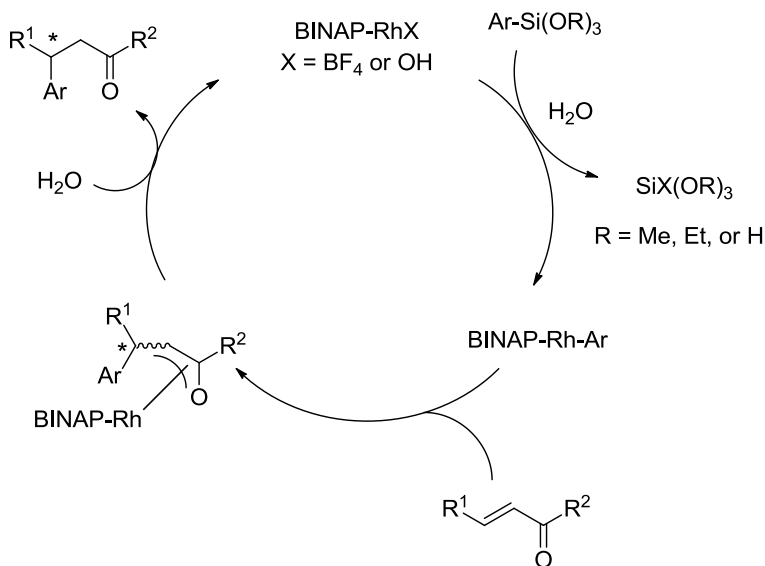
(entry 7) arylsilanes readily form  $\beta$ -substituted products with identical and impressive enantiomeric excess. *E*- and *Z*-styrylsilanes proceed without isomerization of olefin geometry (entries 10 and 11) in good yield with ees of 91 % and 87 % respectively.

**Table1. Rhodium-catalyzed 1,4 addition of organosiloxanes to  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>60</sup>**

$\text{R-Si(OR')}_3 + \text{R}^1\text{-CH=CH-C(=O)R}^2 \xrightarrow[\text{dioxane/H}_2\text{O, 90 }^\circ\text{C, 20 h}]{[\text{Rh(cod)(MeCN)}_2]\text{BF}_4, \text{ (S)-BNAP}} \text{R}^1\text{-CH(R)-CH}_2\text{-C(=O)R}^2$				
entry	silane	electrophile	yield %	ee %
1			76	98
2			89	94
3			90	75
4			62	98
5			93	90
6			75	81
7			56	96
8			73	96
9			54	96
10			85	91
11			88	87

Mechanistic details have not been thoroughly investigated for this rhodium-catalyzed transformation. The  $\beta$ -substituted product may result from a catalytic cycle (Scheme 11) that involves transmetalation between a rhodium complex and the organosilane reagent.<sup>60</sup> Transmetalation results in an organorhodium intermediate that can insert into the carbon-carbon double bond of the  $\alpha,\beta$ -unsaturated carbonyl compound. The resulting rhodium enolate may then protonate, regenerating an active rhodium hydroxide complex.

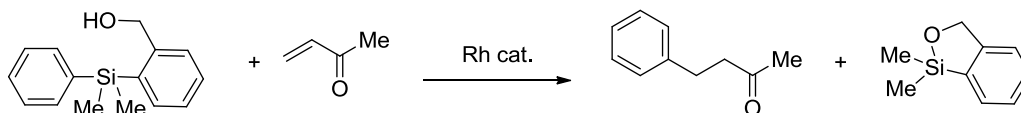
**Scheme 12. Presumed reaction pathway of rhodium-catalyzed 1,4 addition of organosiloxanes to  $\alpha,\beta$ -unsaturated carbonyl compounds. Figure adapted from reference 60.**



In 2007 Hiyama and coworkers demonstrated that alkenyl-, aryl-, and silyl[2-(hydroxymethyl)phenyl]-dimethylsilanes, undergo 1,4-addition reactions to  $\alpha,\beta$ -unsaturated carbonyl compounds under mild rhodium catalysis (Scheme 12).<sup>59</sup> The use of chemically stable

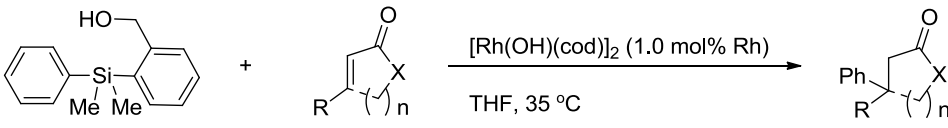



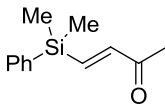
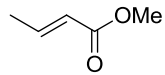
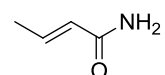
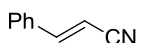
organo[2-(hydroxymethyl)phenyl]dimethylsilanes permits fluoride-free silicon-rhodium transmetalation to occur. The proximal hydroxyl group may coordinate to silicon in the presence of mild bases, such as  $K_2CO_3$ , to produce a pentacoordinate silicate required for successful transmetalation.

**Scheme 13. Organo[2-(hydroxymethyl)phenyl]dimethylsilanes as mild agents for rhodium-catalyzed 1,4 addition of organosiloxanes to  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>59</sup>**



The scope of this rhodium-catalyzed reaction is remarkably broad. Numerous electrophiles undergo successful coupling (Table 2), including enones (entries 1-4), enoates (entry 5), vinyl cyanides (entry 7), and  $\alpha,\beta$ -unsaturated amides (entry 6). Even electrophiles bearing silyl groups (entry 4) provide excellent yields, demonstrating the selective nature of this methodology.

**Table 2. Rhodium-catalyzed 1,4 addition of organosilanes to various electrophiles<sup>59</sup>**

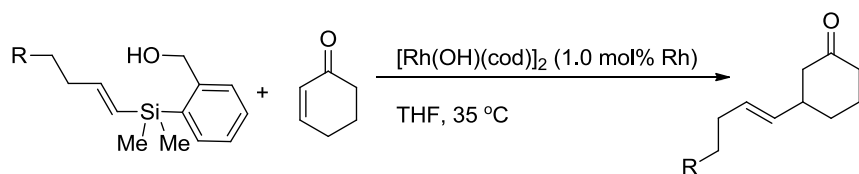
		
entry	electrophile	yield %
1	 n =1	94
2	 n=2	95
3	 n=3	86
4		90
5		86
6		80
7		94

Vinylsilanes, of various olefin substitution patterns, including tri-substituted and  $\alpha$ -substituted vinylsilanes, undergo clean 1,4-addition.<sup>59</sup> This work highlights limitations in extant boron methodology because the corresponding vinylboronic acids are thermally unstable thus, have rarely been employed in rhodium-catalyzed transformations.

Excellent chemoselectivity is observed in the presence of functional groups such as cyano, siloxy, ester, halide, and phthalimide (Table 3).<sup>59</sup> Even enolizable malonates and free hydroxyl groups participate providing yields as high as 91% and 81 % respectively. These vinyl silanes are readily available from platinum-catalyzed hydrosilylation of the corresponding alkynes.



**Table 3. Functional-group-tolerance of rhodium-catalyzed 1,4 addition of vinylsilanes to 2-cylcohexenone<sup>59</sup>**



entry	R	yield %
1	OSiMe <sub>2</sub> tBu	94
2	CN	87
3	CO <sub>2</sub> Me	89
4	Cl	94
5	PhthN	84

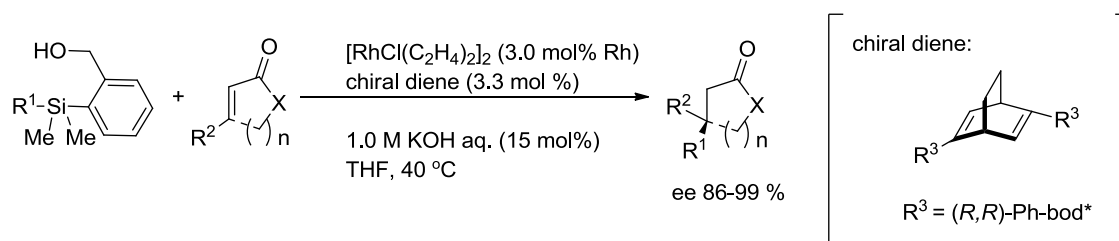
Many arylsilanes containing a variety of functional groups commonly thought of as susceptible in the complementary palladium chemistry<sup>61</sup> remain intact during the reaction (Table 4).<sup>59</sup> Arylsilanes containing electron withdrawing groups (entries 2-4 ) and electron donating groups (entries 1 and 6) exhibit good reactivity. The reaction met success in the presence of an arylbromide containing substrate (entry 4). Ortho-substitution is often troublesome in rhodium-catalyzed reactions, but the reaction proceeds smoothly for a sterically demanding mesitylsilane (entry 6). Noteworthy is the tolerance of the reaction for a boryl-containing arylsilane (entry 5). This selectivity would not likely be observed under fluoride-free palladium conditions.<sup>61</sup>

**Table 4. Rhodium-catalyzed 1,4 addition of arylosilanes to 2-cyclohexenone<sup>61</sup>**

entry	silane	yield
1		96
2		89
3		90
4		93
5		69
6		85

Rhodium-catalyzed reactions which provide excellent enantioselectivities were achieved by employing the chiral diene ligand (1*R*,4*R*)-2,5-diphenylbicyclo[2.2.2]-octa-2,5-diene [(*R,R*)-Ph-bod\*] (Scheme 13).<sup>59</sup> The enantioselective variation appears to be general for a variety of both silyl-nucleophiles and  $\alpha,\beta$ -unsaturated carbonyl compounds.

#### Scheme 14. Enantioselective rhodium-catalyzed 1,4 addition<sup>61</sup>



There appear to be significant advantages to the rhodium methodology<sup>59</sup> over similar transformations with organosilanes and palladium catalysis.<sup>61</sup> The overall scope of the rhodium methodology is far more extensive. The yields are much higher in many cases due to the lack of Heck-type byproducts from  $\beta$ -hydride elimination often encountered with palladium catalysis.<sup>61</sup> As discussed previously, this class of organosilane nucleophiles exhibit superior thermal stability to their organoboron counterparts.

## 2.5 Conclusion

Organometallic reagents continue to play a major role in the elaboration of new methodologies in organic synthesis. Reliable access organosilanes has given organic chemist significant tools to tackle synthetic obstacles often encountered when employing other nucleophilic coupling partners. The diversity of uses for silicon groups ensure that they will continue to find extensive utilization. The reaction systems presented here, while truly significant, merely provide a glimpse into the areas of greatest development in organosilicon chemistry in organic synthesis.

## 2.6 References

- (1) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432.
- (2) Denmark, S. E.; Muhuhi, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 11768.

- (4) Handy, C. J.; Manoso, A. S.; McElroy, W. T.; Seganish, W. M.; DeShong, P. *Tetrahedron* **2005**, *61*, 12201.
- (5) Seganish, W. M.; DeShong, P. *Org. Lett.* **2006**, *8*, 3951.
- (6) Trost, B. M.; Ball, Z. T. *Synthesis-Stuttgart* **2005**, 853.
- (7) Hatanaka, Y.; Goda, K.; Hiyama, T. *Tetrahedron Lett.* **1994**, *35*, 1279.
- (8) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
- (9) Denmark, S. E.; Regen, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486.
- (10) Okazaki, Y.; Rao, S.; Asao, S.; Tateishi, T. *Materials Transactions Jim* **1998**, *39*, 1070.
- (11) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.
- (12) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1989**, *54*, 268.
- (13) Hiyama, T. *Organosilicon Compounds in Cross-Coupling Reactions. In Metal Catalyzed Cross-Coupling Reactions; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany* **1998**, Chapter 10.
- (14) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137.
- (15) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266.
- (16) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684.
- (18) Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051.
- (19) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053.
- (20) Denmark, S. E.; Sweis, R. F. *Chemical & Pharmaceutical Bulletin* **2002**, *50*, 1531.
- (21) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.
- (22) Shukla, K. H.; DeShong, P. *J. Org. Chem.* **2008**, *73*, 6283.
- (23) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793.
- (24) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2004**, *126*, 4876.
- (25) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865.

- (26) Shukla, K. H.; DeShong, P. *J. Org. Chem.* **2008**, *73*, 6283.
- (27) Kurosawa, H.; Emoto, M.; Ohnishi, H.; Miki, K.; Kasai, N.; Tatsumi, K.; Nakamura, A. *J. Am. Chem. Soc.* **1987**, *109*, 6333.
- (28) Kurosawa, H.; Emoto, M.; Urabe, A.; Miki, K.; Kasai, N. *J. Am. Chem. Soc.* **1985**, *107*, 8253.
- (29) Becerra, R. *The Chemistry of Organic Silicon Compounds* **1998**, Rappoport, Z., Apeloig, Y., Eds.; Wiley: Chichester, UK, 153.
- (30) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* **2000**, *2*, 2491.
- (31) Denmark, S. E.; Neuville, L. *Org. Lett.* **2000**, *2*, 3221.
- (32) Denmark, S. E.; Pan, W. *Org. Lett.* **2000**, *3*, 61.
- (33) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565.
- (34) Franz, A. K.; Woerpel, K. A. *Journal of the American Chemical Society* **1999**, *121*, 949.
- (35) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Organic Letters* **2001**, *3*, 3811.
- (36) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Journal of Organic Chemistry* **2002**, *67*, 8450.
- (37) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138.
- (38) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536.
- (39) Herron, J. R.; Ball, Z. T. *J. Am. Chem. Soc.* **2008**, *130*, 16486.
- (40) Lee, K.-S.; Hoveyda, A. H. *J. Org. Chem.* **2009**, *74*, 4455.
- (41) Herron, J. R.; Russo, V.; Valente, E. J.; Ball, Z. T. *Chem. Eur. J.* **2009**, *15*, 8713.
- (42) Russo, V.; Herron, J. R.; Ball, Z. T. *Org. Lett.* **2010**, *12*, 220.
- (43) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853.

- (44) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.
- (45) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
- (46) Tanyeli, C.; Akhmedov, I. M.; Ozdemirhan, D. *Enantiomer* **2001**, *6*, 259.
- (47) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.
- (48) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, UK, 1992J.
- (49) Petrier, C.; Barbosa, J. C. D.; Dupuy, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 5761.
- (50) Eshelby, J. J.; Crowley, P. J.; Parsons, P. J. *Synlett* **1993**, 279.
- (51) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053.
- (52) Flemming, S.; Kabbara, J.; Nickisch, K.; Neh, H.; Westermann, J. *Synthesis-Stuttgart* **1995**, 317.
- (53) Westermann, J.; Nickisch, K. *Angew. Chem. Int. Ed.* **1993**, *32*, 1368.
- (54) Huang, T. S.; Meng, Y.; Venkatraman, S.; Wang, D.; Li, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 7451.
- (55) Huang, T. S.; Venkatraman, S.; Meng, Y.; Nguyen, T. V.; Kort, D.; Wang, D.; Ding, R.; Li, C. J. *Pure Appl. Chem.* **2001**, *73*, 1315.
- (56) Venkatraman, S.; Li, C. J. *Tetrahedron Lett.* **2001**, *42*, 781.
- (57) Venkatraman, S.; Meng, Y.; Li, C. J. *Tetrahedron Lett.* **2001**, *42*, 4459.
- (58) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91.
- (59) Nakao, Y.; Chen, J.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W.-L.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 9137.

- (60) Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667.
- (61) Denmark, S. E.; Amishiro, N. *J. Org. Chem.* **2003**, *68*, 6997.

# Chapter 3

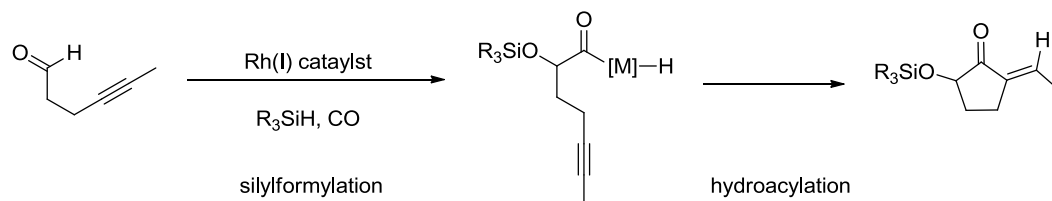
## **Rhodium-catalyzed tandem silylformylation-hydroacylation of 4-alkynals**

### **3.1 Introduction**

Transition-metal-catalyzed tandem carbon-carbon bond formations are powerful methods for the synthesis of structurally complex molecules from relatively simple starting materials in a convergent way. Molecules that have two or more different unsaturated bonds are particularly interesting substrates for the tandem reactions involving multiple C-C bond formations with a single catalyst in one operation, allowing the construction of a variety of cyclic compounds. Aldehyde substrates containing tethered alkynes present an entry point to combine silylformylation and hydroacylation in an intramolecular way to construct a cyclic skeleton (Scheme 1). Although many rhodium(I)-catalyzed tandem reactions have been reported,<sup>1-6</sup> none combining these two powerful reactions are present in the literature.

**Scheme 1. Proposed tandem silylformylation-hydroacylation transformation**

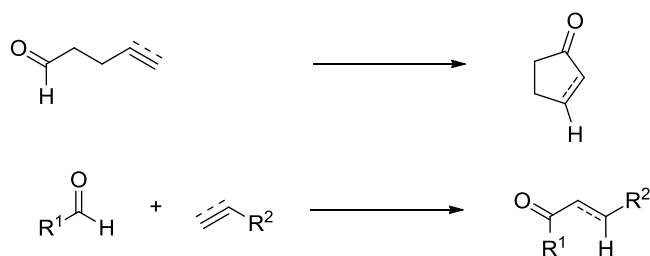




### 3.1.1 Hydroacylation

The catalytic activation and subsequent functionalization of C-H bonds is an attractive goal for synthetic chemists, with reactions that employ low catalyst loadings and result in the formation of C-C bonds being of particular interest. The hydroacylation<sup>1</sup> of alkenes and alkynes are transformations that fulfill these requirements; in addition, these processes are inherently atom-economic and can be catalyzed by a variety of transition metals. Hydroacylation formally involves the addition of an acyl unit and a hydrogen atom across a C-C multiple bond; intra- and intermolecular variants of the reactions are known (Scheme 2).<sup>2-4</sup>

#### Scheme 2. Hydroacylation



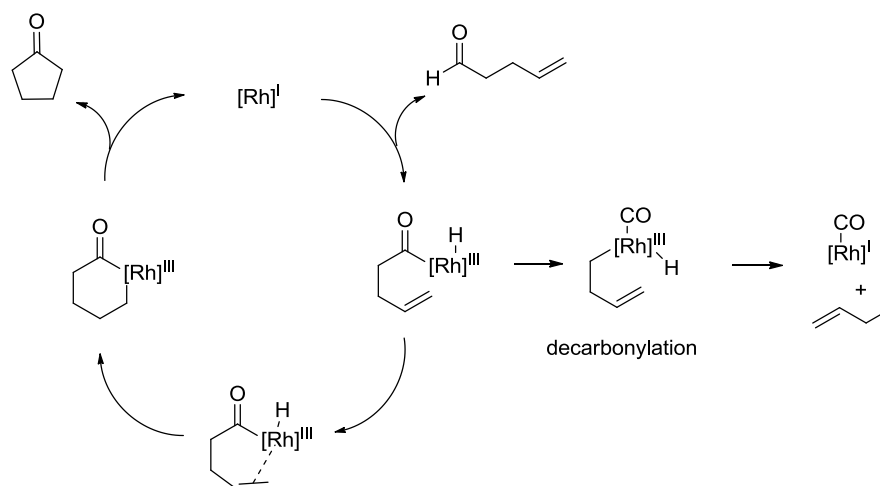
Intramolecular alkene hydroacylation using a stoichiometric amount of a rhodium catalyst and resulting in the formation of a cyclopentanone was first reported by Sakai and co-

workers in 1972. Since this first report, significant advances have been achieved.<sup>5</sup> Intramolecular alkene hydroacylation can now be performed using low catalyst loadings under mild reaction conditions.<sup>6</sup> In addition, for cyclopentanone syntheses, the use of enantiomerically pure catalysts allows highly enantioselective reactions to be performed.<sup>7</sup> The combination of these developments has resulted in intramolecular alkene hydroacylation being applied to a number of target syntheses. Intermolecular alkyne hydroacylation is a less advanced reaction although a number of systems that employ low catalyst loadings and mild conditions have been developed.<sup>8-</sup>

11

A number of mechanistic studies have been reported,<sup>12</sup> however, a brief mention of the reaction mechanism is warranted here. A basic, generally accepted, catalytic cycle for an intramolecular hydroacylation reaction is shown below (Scheme 3). The key steps involve oxidative addition of the metal catalyst across the aldehyde C-H bond to generate an acyl metal hydride, subsequent addition across the alkene, followed by reductive elimination to generate a ketone product and regenerate the catalyst. The main limitation of hydroacylation as a synthetically useful reaction stems from the general propensity of acyl metal species to undergo reductive decarbonylation. This produces reduced substrates and poorly active carbonylated catalysts. This type of decarbonylation is such a facile process that a number of synthetically useful methods based on this reaction are known. In general, the most significant advances in hydroacylation chemistry have involved developing strategies, or methods, to limit this undesired decarbonylation pathway.<sup>2,3,13,14</sup>

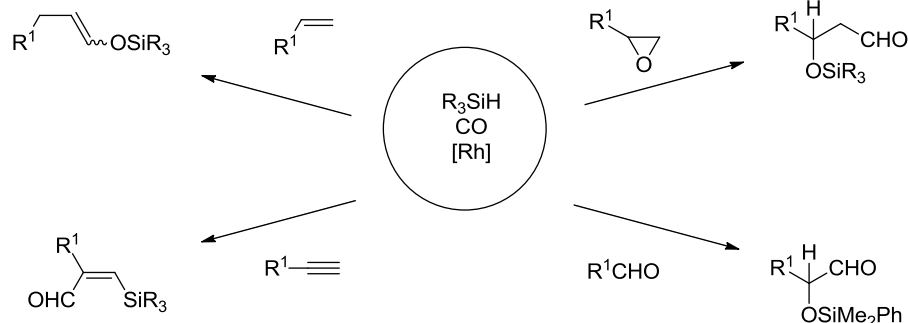
### **Scheme 3. Traditional hydroacylation mechanism**



### 3.1.2 Silylformylation

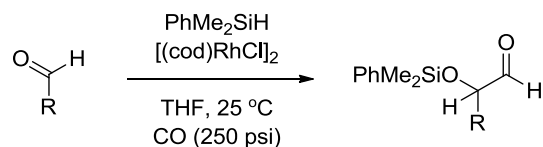
In addition to atom economy, the use of cheap, readily available feedstock materials for specific transformations is a common goal in organic chemistry. Catalytic incorporation of carbon monoxide is one of the most elegant synthetic tools for the direct introduction of a carbonyl group into organic molecules. Rhodium(I)-catalyzed silylformylation (Scheme 4) is a powerful reaction that is defined as the addition of  $R_3Si$ - and  $-CHO$  across various types of bonds using a silane ( $R_3SiH$ ), CO and a transition metal catalyst.<sup>15</sup> This transformation not only incorporates carbon monoxide, it also utilizes organosilanes and the benefits associated with this class of molecules (section 2.1).

**Scheme 4. Silylformylation**



Rhodium(I)-catalyzed silylformylation of carbonyl compounds was presented by Wright and Cochran in 1993 (Scheme 5).<sup>16</sup> In their report, aromatic-, heteroaromatic-, and aliphatic aldehydes selectively undergo silylformylation to provide the corresponding  $\alpha$ -siloxyaldehydes under an atmosphere of carbon monoxide (250 psi) in the presence of a rhodium(I) precatalyst and dimethylphenylsilane. Interestingly, this reaction tolerates the presence of internal alkene, alkyne, ester, and acyclic ketone functional groups.

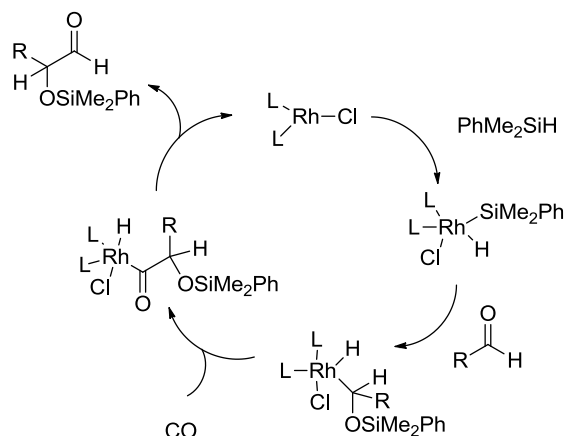
#### Scheme 5. Silylformylation of aldehydes



A generalized catalytic cycle for the silylformylation of benzaldehyde is illustrated below (Scheme 6).<sup>16,17</sup> Oxidative addition of rhodium(I) into the Si-H bond is followed by coordination of the aldehyde. Migratory insertion of the silyl-rhodium-hydride into the aldehyde provides an  $\alpha$ -siloxyalkyl-rhodium hydride. Subsequent formation of the rhodacyl hydride complex is provided

via a facile insertion of CO into the alkyl-metal bond which then undergoes reductive elimination that results in an  $\alpha$ -siloxyaldehyde and an active rhodium(I) species.

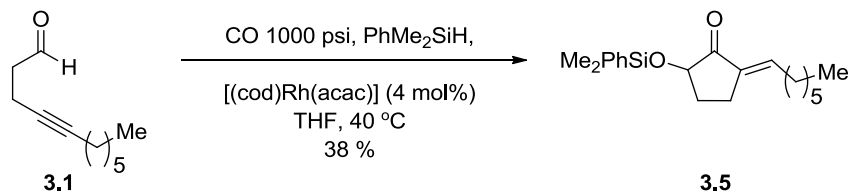
### Scheme 6. Silylformylation of aldehydes mechanism



### 3.2 Tandem hydroacylation-silylformylation

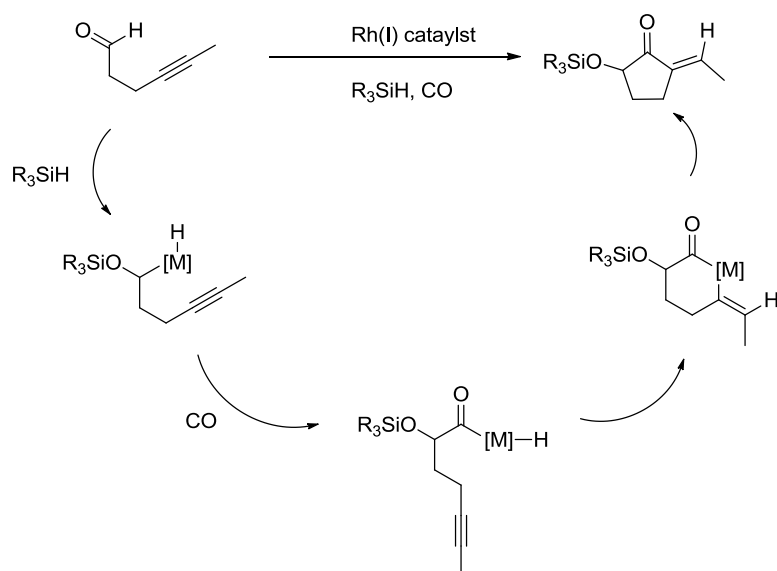
A tandem process incorporating both hydroacylation and silylformylation methodologies with aldehydes and tethered alkynes would provide for the rapid construction of very complex molecules in one pot. Given that rhodium-catalyzed silylformylation of aldehydes generally occurs more rapidly and at lower temperatures than hydroacylation we chose to pursue the potential of this tandem reaction. At the time this work was conducted, there were no reports of such tandem reactions, and there remain no alternate methods to rapidly prepare **3.5** from such simple starting materials. In this chapter we establish that rhodium(I) complexes catalyzed a novel tandem silylformylation-hydroacylation of 4-alkynals with carbon monoxide and hydrosilanes up to a 38% yield (Scheme 6).

**Scheme 7. Rhodium-catalyzed tandem silylformylation-hydroacylation of undec-4-ynal**



Our working hypothesis for the mechanism of this novel tandem process is illustrated in Scheme 7. We believe that like silylformylation,  $\text{Rh}(\text{I})$  will oxidatively insert into the H-Si bond forming a double bond of the silyl(hydrido) metal species should then result in an  $\alpha$ -siloxyalkyl rhodium hydride. Subsequent formation of the rhodacyl hydride complex is provided via a facile insertion of CO into the alkyl-metal bond. Complexation of the alkyne, followed by migratory insertion, then provides the six-membered rhodium metalocycle. Reductive elimination furnishes the  $\alpha$ -siloxyketone and regenerates the rhodium(I) catalyst. Since the Ojima-Crabtree hydrosilylation mechanism is not operative under CO atmosphere, undesired rhodium-catalyzed hydrosilylation of areas of unsaturation should not be expected to form.<sup>18</sup>

**Scheme 8. Proposed mechanism for tandem silylformylation-hydroacylation**



### 3.2.1 Substrate synthesis

To avoid complications with regioselectivity and possible competing hydroacylation we initially focused our attention on 4-alkynals. Tanaka and coworkers found that when TMSI was employed for the copper-promoted 1,4-addition of terminal alkynes to  $\alpha,\beta$ -unsaturated aldehyde provided clean access to 4-alkynals.<sup>4,19,20</sup> Using this previously developed method, three 4-alkynals were synthesized (Table 1). Yields were typically modest ranging from 26-61% (Table 1, entries 1-3, **3.1-3.3**).

**Table 1. Synthesis of 4-alkynals**

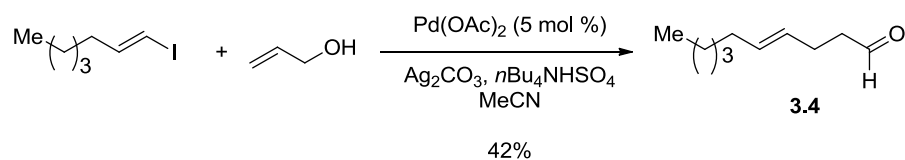
entry	aldehyde	alkyne	product	number	yield %
1				<b>3.1</b>	61
2				<b>3.2</b>	55
3				<b>3.3</b>	26

All reactions performed with  $\alpha,\beta$ -unsaturated aldehyde with 1.0 eq of alkyne, 1.0 eq of *n*BuLi, 1.1 eq CuI, and 1.2 eq TMSI under an atmosphere of nitrogen. Reactions were generally complete after 4 h.

We also hoped to investigate this reaction with respect to 4-alkenals. An alkene substrate **3.4** was acquired through a Heck coupling of allyl alcohol and a vinyl iodide (Scheme 8). Several copper-promoted conjugate addition reactions are also available for this transformation, but in our hands the reactions were low yielding and did not offer significant benefits over the single-step procedure below.



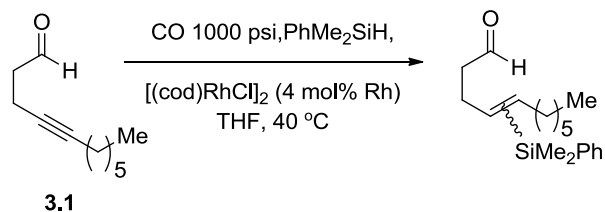
### Scheme 9. Synthesis of alkenal 3.4



### 3.2.2 Reaction optimization

Investigations were initiated by placing all reagents into a Parr bomb at room temperature. The par bomb was then placed under a 1000 psi atmosphere of carbon monoxide and heated for 12 h. Initial attempts to perform this reaction were unsuccessful due to competing hydrosilylation of the alkyne (Scheme 9).

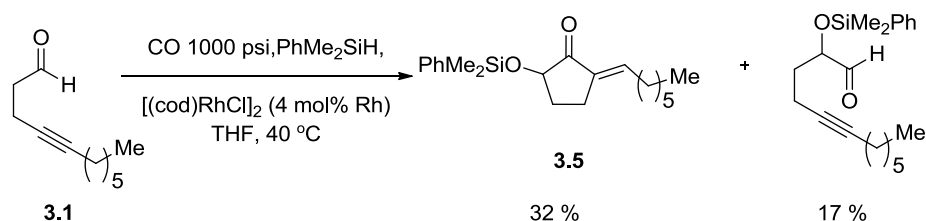
### Scheme 10. Undesired hydrosilylation



To avoid hydrosilylation, the setup was modified by cooling the Parr bomb to -78 °C before adding silane under an atmosphere of nitrogen. We were extremely gratified to find that

substrate **3.1** provided 32 % of the desired product **3.5** accompanied by 17 % of silylformylation product (Scheme 10). This initial result compelled us to pursue the process further.

### Scheme 11. Initial tandem reaction results



A quick screen of reactions temperatures was conducted (Table 2). The results suggest that warming the Parr bomb to 40 °C provides the optimum reaction temperature. Lower and higher temperatures only led to decreased yields of product **3.5**. Reaction yields were obtained by employing 1,4-trimethoxybenzene as an internal standard for <sup>1</sup>H NMR. The olefin proton of **3.5** was used as the diagnostic handle.

**Table 2. Optimization of reaction temperature**

entry	temperature °C	yeild <sup>a</sup> (NMR)
1	0	17
2	rt	24
3	40	28
4	60	20
5	80	7

<sup>a</sup> Yields determined by NMR with 1,4-dimethoxybenzene as internal standard.

We had hoped that the increased catalyst loading would increase the reaction yield (Table 3). Unfortunately, this effect was not observed. Lowering the catalyst loading to 2 mol % rhodium did not offer any benefit to the yield either.

**Table 3. Optimization of catalyst loading**

Reaction scheme: 3.1  $\xrightarrow[\text{THF, 40 } ^\circ\text{C}]{\text{CO 1000 psi, PhMe}_2\text{SiH, } [(\text{cod})\text{RhCl}]_2 \text{ (X mol\% Rh)}}$  3.5

entry	mol % Rh	yeild <sup>a</sup> (NMR)
1	2	22
2	4	28
3	6	23
4	8	12

<sup>a</sup> Yields determined by NMR with 1,4-dimethoxybenzene as internal standard.

During the course of reaction optimization, the system was examined with respect to solvent. Only when the solvents were dry and degassed did the reaction proceed. As a result of these investigations, THF became the solvent of choice for the tandem reaction. Other coordinating solvents were examined, but these solvents (Table 4, entries 2 and 3) did not amplify the yield.

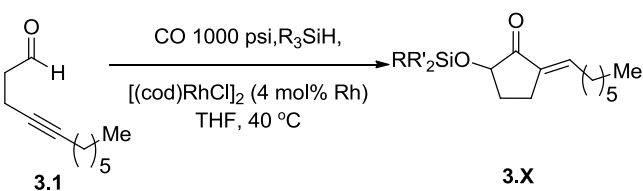
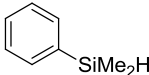
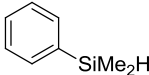
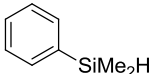
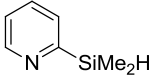
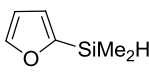
**Table 4. Solvent screening**

entry	solvent	yield <sup>a</sup> (NMR)
1	THF	28
2	dioxane	23
3	MeCN	6
4	CH <sub>2</sub> Cl <sub>2</sub>	0

<sup>a</sup> Yields determined by NMR with 1,4-dimethoxybenzene as internal standard.

We investigated the reaction to with a slight excess of silane and found that better yields could be obtained over 12 h at 40 °C (Table 5, entry 2.). Consistent with silylformylation of aldehydes,<sup>16,17</sup> studies on the scope of the tandem reaction showed that this process is also limited to PhMe<sub>2</sub>SiH and Ph<sub>2</sub>MeSiH. Attempts to employ silanes containing chelating groups were unsuccessful providing only decomposition products (Table 5, entries 6 and 7).

**Table 5. Optimization of silane loading**

			
entry	silane	eq silane	yeild <sup>a</sup> (NMR)
1		1.0	28
2		1.2	32
3		3.0	12
4	MePh <sub>2</sub> SiH	1.2	18
5	Me <sub>3</sub> SiH	1.0	0
6		1.0	0
7		1.0	0

<sup>a</sup> Yields determined by NMR with 1,4-dimethoxybenzene as internal standard.

A slight increase in steric bulk around the alkyne **3.2** proved to be amenable to the reaction (Table 6, entry 2). Regrettably, the other substrates proved to be less tolerant of the reaction conditions. We had hoped that substrate **3.3** containing a hemilabile benzyloxy group (Table 6, entry 3) would increase the reaction yield by offering additional stabilization to a rhodium(III) intermediate, unfortunately this was not observed. Alkene substrate **3.4** was unreactive to the standard conditions (Table 6, entry 4). The reasons for the lack of reactivity

with alkenes are unclear, though there are some indications in the crude NMR that decarbonylation may have occurred.

**Table 6. Reaction scope**

entry	number	aldehyde	product number	yield <sup>a</sup> (NMR)
1	3.1		3.5	32
2	3.2		3.6	22
3	3.3		3.7	6
4	3.4		3.8	0

<sup>a</sup> Yields determined by NMR with 1,4-dimethoxybenzene as an internal standard.

We imagined that the problems of low yield to be due to catalyst decomposition. Since the reaction was under 1000 psi CO and could not be opened we turned to the idea of using ligands to stabilize rhodium (Table 7). A variety of ligands were examined including nitrogen-based ligands, phosphines, arsines, and other dienes. In the Wright reports,<sup>16,17</sup> phosphine ligands, both mono and bidentate, inhibit the rhodium-catalyzed silyformylation whereas nitrogen-based ligands like 2,2'-bipyridine can be used at high ligand to metal ratios. While in most cases the tandem reaction proceeded, ligands did not offer improved yields over the original conditions without ligand (32% without ligand, Table 6, entry 1) both phosphines and nitrogen-based ligands alike. Bidentate phosphine ligands of appropriate bite angle (Table 7, entries 4-7) provided yields ranging from 28-32%. Pyridine and 2,2'-BIPY provided yields of 20 and 22% respectively (Table 7, entries 1 and 2). Attempts to increase the reaction yield with ligand additives were unsuccessful. It became apparent that a different rhodium catalyst was required to improve reaction yield.

Table 7. Synthesis of 4-alkynals

<p> <math>\text{CO 1000 psi, Me}_2\text{PhSiH,}</math>  <math>[(\text{cod})\text{Rh}(\text{acac})] \text{ (4 mol\%)} \rightarrow</math>  <math>\text{ligand (X mol \%)}</math>  <math>\text{THF, 40 } ^\circ\text{C}</math> </p>			
entry	ligand	mol %	yield <sup>a</sup> (NMR)
1		8	20
2		4	22
3		4	10
4		4	30
5		4	32
6		4	28
7		4	30
8		4	0
9		4	20
10	$\text{Ph}_3\text{As}$	8	0
11	$\text{Ph}_3\text{P}$	8	15



<sup>a</sup> Yields determined by NMR with 1,4-dimethoxybenzene as an internal standard.

Despite the great reproducibility of the tandem reactions, yields were consistently low. In an attempt to remedy this deficiency, a screening of rhodium(I) catalyst was conducted. This study did result in a slight increase in yield (Table 8, entry 2), but this success was short lived. After screening a variety of rhodium(I) sources, the yield was only increased to 38%.

**Table 8. Optimization of rhodium catalyst**

entry	mol % Rh	yeild <sup>a</sup> (NMR)
1	[(cod)RhCl] <sub>2</sub>	32
2	[(cod)Rh(acac)]	38
3	[(CO)RhCl] <sub>2</sub>	0
4	[(cod)RhBF <sub>4</sub> ] <sub>2</sub>	15
5	[(CO) <sub>2</sub> Rh(cp*)]	26

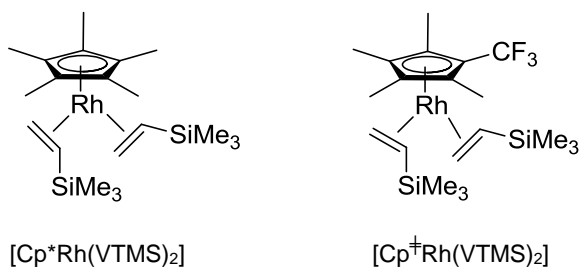
<sup>a</sup> Yields determined by NMR with 1,2-dimethoxybenzene as an internal standard.

### 3.3 Future directions

The lack of success in regards to increasing reaction yield of the tandem cascade naturally leads to the goal of locating the right catalyst. In 2006, Brookhart and coworkers demonstrated that use of the more electron-deficient catalyst [Cp<sup>†</sup>Rh(VTMS)<sub>2</sub>] (Cp<sup>†</sup> = C<sub>5</sub>Me<sub>4</sub>CF<sub>3</sub> vs. Cp\* = C<sub>5</sub>Me<sub>5</sub>) (Figure 1) results in faster rates, better selectivity for the intermolecular

hydroacylation of aromatic aldehydes to olefins.<sup>21</sup> Mechanistic studies suggested that  $[\text{Cp}^{\ddagger}\text{Rh}(\text{VTMS})_2]$  displayed a faster turnover frequency (relative to  $[\text{Cp}^*\text{Rh}(\text{VTMS})_2]$ ) because of an increase in the rate of reductive elimination, the turnover-limiting step, from the more electron-deficient metal center of  $[\text{Cp}^{\ddagger}\text{Rh}(\text{VTMS})_2]$ .

**Figure 1. Brookhart catalysts**



Since our efforts to employ  $\text{Cp}^*$  ligands for rhodium (Table 8, entry 5) were comparable to pseudo-optimized tandem reaction conditions (Table 8, entry 2), we believe that this modification to the  $\text{Cp}^*$  ligand would offer increased benefits to our system as well.

### 3.4 Conclusions

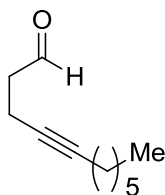
In this chapter we demonstrate the first example of a tandem silylformylation-hydroacylation catalyzed by rhodium(I). The reaction system presented here provides a modest access to  $\alpha$ -silyloxy cyclic enones from a number of 4-alkynals. As we have previously noted, the observed low yields are especially troubling. Our understanding of the precise conditions necessary to optimize this reaction is still in its infancy, and it may be possible to improve yields and scope with better understanding of subtle factors responsible for the desired transformation.

### 3.5 Experimental

General information: Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Copper iodide, PdOAc<sub>2</sub>, [(cod)RhCl]<sub>2</sub>, [(cod)Rh(acac)], [(CO)RhCl]<sub>2</sub>, [(cod)RhBF<sub>4</sub>]<sub>2</sub>, [(CO)Rh(cp\*)], 1,1-Bis(diphenylphosphino)methane, 1,2-Bis(diphenylphosphino)ethane, 1,3-is(diphenylphosphino)propane, 1,1'-Bis(diphenylphosphino)ferrocene, and bis[2-(diphenylphosphino)phenyl] ether were purchased from Strem Chemicals, Inc. and used without further purification. Pyridine, acrolein, crotonaldehyde, and norbornadiene were purchased from Aldrich Chemical Co. and distilled before using. 1-octyne was purchased from GFS Chemicals and used as received. Benzyl bromide, triphenylphosphine, 2,2'-bipyridine, 1,3,5-trimethoxybenzene, triphenylarsine, 3-buten-1-ol, NaH (60% in mineral oil), isobutyraldehyde, glyoxal, 2,6-diisopropylaniline, trimethylsilane, and paraformaldehyde were purchased from Acros Organics and used as received. UHP carbon monoxide was purchased from Matheson Gas and used as received. 3-Butenyl ether,<sup>22</sup> 2-isopropylacrolein,<sup>23</sup> dimethyl(2-pyridyl)silane,<sup>24</sup> (2-furyl)dimethylsilane,<sup>25</sup> and N,N'-bis(2,6-diisopropylphenyl)-1,4-diaza-1,3-butadiene<sup>26</sup> prepared on multi-gram scale according to procedures described in the literature. THF, ether, and dioxane were distilled from sodium benzophenone ketyl under nitrogen. Acetonitrile and dichloromethane were distilled from calcium hydride under nitrogen. Flash chromatography was performed with 40-63  $\mu$ m particle size silica gel. NMR data were acquired with Bruker Avance 400 MHz or Bruker Avance 500 MHz instruments. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded relative to residual solvent.

Tandem reactions were carried out in a Parr stainless steel pressure vessel equipped with a pressure gauge, as inlet, and pressure release valve according to the general procedure 2.

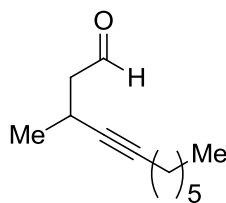
### Undec-4-ynal, **3.1**



**General procedure 1:** *n*-BuLi (2.5 M in hexane, 12.4 mL, 30.9 mmol) was added to a stirred solution of 1-octyne (4.0 mL, 30.8 mmol) in THF (90 mL) at -78 °C. The resulting mixture was stirred for 25 min before warming to 0 °C. CuI·0.75 SMe<sub>2</sub> (8.46 g, 35.7 mmol) was added to the mixture and stirred for 1 h. After cooling to -78 °C, TMSI (4.8 mL, 33.7 mmol) was added, and the resulting mixture was stirred at -78 °C for 5 min. Acrolein (2.1 mL, 31.4 mmol) was added at -78 °C, and the resulting mixture was stirred at -45 °C for 2 h. The reaction was quenched by the addition of saturated aqueous NH<sub>4</sub>Cl and extracted with Et<sub>2</sub>O. The organic layer was washed with 5% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (hexane:EtOAc = 50:1), which furnished undec-4-ynal (**3.1**, 3.1 g, 18.8 mmol, 61% yield) as a pale yellow oil. Spectral data matched that of the known compound.<sup>27</sup>

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.80 (t,  $J = 1.5$  Hz, 1H), 2.62 (tt,  $J = 6.9$  and 1.5 Hz, 2H), 2.44-2.53 (m, 2H), 1.72-1.77 (m, 2H), 1.44-1.52 (m, 2H), 1.24-1.40 (m, 6H), 0.89 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  201.8, 81.5, 77.7, 33.6, 31.6, 29.3, 28.8, 22.8, 18.9, 18.8, 14.3.

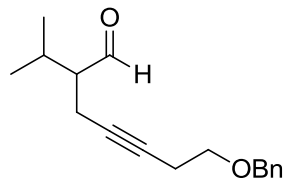
### 3-Methylundec-4-ynal, 3.2



The title compound was prepared as a pale yellow oil in 55 % from 1-octyne and crotonaldehyde according to general procedure 1. Spectral data matched that of the known compound.<sup>19</sup>

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  9.80 (t,  $J = 2.1$  Hz, 1H), 2.89-3.02 (m, 1H), 2.53 (ddd,  $J = 16.5$ , 7.5, and 2.1 Hz, 1H), 2.45 (ddd,  $J = 16.5$ , 7.5, and 2.1 Hz, 1H), 2.12 (dt,  $J = 6.9$  and 2.1 Hz, 2H), 1.24-1.48 (m, 8H), 1.20 (d,  $J = 6.9$  Hz, 3H), 0.90 (t,  $J = 6.9$  Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  202.2, 82.6, 82.0, 50.5, 31.4, 29.2, 28.7, 22.8, 21.6, 21.1, 19.0, 14.2.

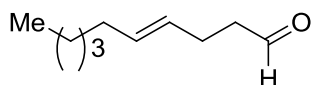
### 7-(Benzyloxy)-2-isopropylhept-4-ynal



The title compound was prepared as a pale yellow oil in 26 % from benzyl 3-butenyl ether<sup>22</sup> and 2-isopropylacrolein<sup>23</sup> according to general procedure 1.

<sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.48 (d,  $J$  = 2.5, 1H), 7.16-7.27 (m, 3H), 7.06-7.11 (m, 2H), 4.27 (s, 2H), 3.37 (t,  $J$  = 6.9 Hz, 2H), 2.31-2.36 (m, 2H), 2.23-2.26 (m, 2H), 1.91 (m, 1H), 1.83 (m, 1H), 0.67 (dd,  $J$  = 15.5, 6.9).

### **(*E*)-Undec-4-enal, 3.6**



DIBAL (36.6 mL, mmol) was added drop-wise to 1-octyne (4.0 g, mmol) in Hexane (36 mL). The resulting mixture was heated to 50 °C and stirred for 3 h. After cooling the solution to room temperature, hexane was removed under reduced pressure. THF (40 mL) was added and the solution was cooled to -50 °C. A solution of I<sub>2</sub> (9.24 g, mmol) in THF (20 mL) was added dropwise and the solution was warmed to room temperature. After stirring for 1 h, the reaction was quenched with 20% H<sub>2</sub>SO<sub>4</sub> and poured into an ice bath. The organic layer was extracted with pentane (100 mL) and washed with 5% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, sat. NaHCO<sub>3</sub>, and brine. The organic layer

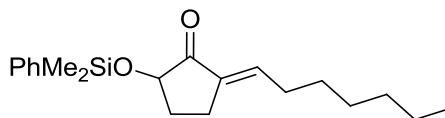
was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and used without purification resulting in 5.6 g of crude material. Spectral data matched that of the known compound.<sup>28</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.51 (dt, *J* = 14.3, 7.0 Hz, 1H), 5.97 (d, *J* = 14.3 Hz, 1H), 2.05 (dt, *J* = 7.0, 6.9 Hz, 2H), 1.45-1.34 (m, 2H), 1.33-1.18 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>) δ 146.78, 74.21, 36.03, 31.56, 28.58, 28.32, 22.54, 14.04.

An oven-dried 250-mL round bottom flask was charged with CH<sub>3</sub>CN (23 mL) purged with nitrogen for 30 min, then Pd(OAc)<sub>2</sub>, Ag<sub>2</sub>CO<sub>3</sub>, *n*-Bu<sub>4</sub>NHSO<sub>4</sub>, allyl alcohol, and (*E*)-1-iodo-1-octene were added. The mixture was stirred at room temperature for 12 h. The mixture was passed through a pad of silica gel, washing with Et<sub>2</sub>O. Removal of the solvent on a rotary evaporator provided an yellow oil, which was purified by silica gel column chromatography (hexane:EtOAc = 50:1), which furnished undec-4-enal (**3.6**, 0.3 g, 1.8 mmol, 42% yield) as a pale yellow oil. Spectral data matched that of the known compound.<sup>29</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.76 (s, 1H), 5.35-5.51 (m, 2H), 2.49 (t, *J* = 7.3 Hz, 2H), 2.33 (q, *J* = 6.2 Hz, 2H), 1.97 (q, *J* = 6.5 Hz, 2H), 1.26-1.36 (m, 10H), 0.88 (t, *J* = 7.1 Hz, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 201.9, 132.0, 127.5, 43.5, 32.4, 31.7, 29.3, 28.8, 25.1, 22.6, 14.0.

**(*E*)-2-((dimethyl)(phenyl)silyl)oxy-5-heptylidencyclopentanone, 3.5**



**General procedure 2:** Under inert atmosphere, a stainless steel pressure vessel equipped with a magnetic stirring bar and a glass liner was charged with **3.1** (84 mg, 0.50 mmol),

[(cod)Rh(acac)] (6.5 mg, 0.02 mmol), and THF (2.5 mL). The vessel was cooled to  $-78\text{ }^{\circ}\text{C}$  followed by addition of dimethylphenylsilane (82 mg, 0.60 mmol). The bomb/pressure gage was assembled and the apparatus was then pressurized to 1000 psi with CO and then vented. This procedure was repeated twice and the apparatus was then pressurized to 1000 psi with CO. The mixture was then heated by immersion in an oil bath set at  $40\text{ }^{\circ}\text{C}$  with magnetic stirring. After 12 hours, the apparatus was cooled to room temperature and then vented. 1,2-dimethoxybenzene (13 mg, 18 % to aldehyde) was added to the mixture followed by removal of the THF under reduced pressure. The crude reaction mixture containing internal standard was then analyzed by  $^1\text{H}$  NMR and the yield was determined to be 38 %. The desired product was then purified by silica gel chromatography (hexane:ethyl acetate = 50:1). The remaining byproducts were removed under reduced pressure resulting in meaningful loss of the desired product. Only 5 mg of material was isolated.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.74-7.74 (m, 2H), 7.20-7.28 (m, 3H), 6.69 (m, 1H), 4.03 (dd,  $J = 11.0$  and  $8.0\text{ Hz}$ , 1H), 2.17 (m, 1H), 1.88 (m, 1H), 1.71-1.79 (m, 2H), 1.61 (m, 1H), 1.07-1.22 (m, 8H), 0.86 (t,  $J = 7.0\text{ Hz}$ , 3H), 0.58 (s, 3H), 0.51 (s, 3H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  202.4, 137.2, 134.5, 134.0, 130.0, 128.1, 127.9, 76.7, 31.7, 29.7, 29.1, 28.3, 21.9, 14.1, -0.5, -1.0.

### 3.6 References

- (1) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725.
- (2) Jun, C. H.; Jo, E. A.; Park, J. W. *Eur. J. Org. Chem.* **2007**, 1869.



- (3) Moxham, G. L.; Randell-Sly, H.; Brayshaw, S. K.; Weller, A. S.; Willis, M. C. *Chem. Eur. J.* **2008**, *14*, 8383.
- (4) Tanaka, K. *J. Synthetic Org. Chem. Jpn.* **2005**, *63*, 351.
- (5) Oonishi, Y.; Mori, M.; Sato, Y. *J. Synthetic Org. Chem. Jpn.* **2007**, *65*, 183.
- (6) Tonks, L.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3637.
- (7) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667.
- (8) Gonzalez-Rodriguez, C.; Pawley, R. J.; Chaplin, A. B.; Thompson, A. L.; Weller, A. S.; Willis, M. C. *Angew. Chem. Int. Ed.* **2011**, *50*, 5134.
- (9) Murphy, S. K.; Coulter, M. M.; Dong, V. M. *Chem. Sci.* **2012**, *3*, 355.
- (10) Parsons, S. R.; Hooper, J. F.; Willis, M. C. *Org. Lett.* **2011**, *13*, 998.
- (11) Vedachalam, S.; Wong, Q. L.; Maji, B.; Zeng, J.; Ma, J. M.; Liu, X. W. *Adv. Synth. Catal.* **2011**, 353, 219.
- (12) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.
- (13) Chung, L. W.; Wu, Y. D. *J. Chem. Theory Comput.* **2005**, *4*, 737.
- (14) Pike, S. D.; Pawley, R. J.; Chaplin, A. B.; Thompson, A. L.; Hooper, J. A.; Willis, M. C.; Weller, A. S. *Eur. J. Inorg. Chem.* **2011**, 5558.
- (15) Aronica, L. A.; Caporusso, A. M.; Salvadori, P. *Eur. J. Org. Chem.* **2008**, 3039.
- (16) Wright, M. E.; Cochran, B. B. *J. Am. Chem. Soc.* **1993**, *115*, 2059.
- (17) Wright, M. E.; Cochran, B. B. *Organometallics* **1996**, *15*, 317.
- (18) Crabtree, R. H. *New J. Chem.* **2003**, *27*, 771.
- (19) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492.
- (20) Tanaka, K.; Fu, G. C. *Org. Lett.* **2002**, *4*, 933.
- (21) Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082.
- (22) Qin, D.-G.; Zha, H.-Y.; Yao, Z.-J. *J. Org. Chem.* **2002**, *67*, 1038.
- (23) Riehs, G.; Urban, E. *Tetrahedron* **1996**, *52*, 1221.
- (24) Itami, K.; Mitsudo, K.; Yoshida, J. *J. Org. Chem.* **1999**, *64*, 8709.

- (25) Stork, G.; Tang, P. C.; Casey, M.; Goodman, B.; Toyota, M. *J. Am. Chem. Soc.* **2005**, *127*, 16255.
- (26) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49.
- (27) Hara, S.; Imai, S.; Hara, T.; Suzuki, A. *Synth. Commun.* **1982**, *12*, 813.
- (28) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.
- (29) Snowden, R. L.; Brauchli, R.; Linder, S. *Helv. Chim. Acta* **2011**, *94*, 1216.

# Chapter 4

## Generation of reactive organocopper species

Parts of this chapter have been adapted from:

Herron, J. R.; Ball, Z. T. "Synthesis and Reactivity of Functionalized Arylcopper Compounds by Transmetalation of organosilanes." *J. Am. Chem. Soc.* **2008**, 130, 16486

Parts of this chapter were in collaboration with Vincenzo Russo and have been adapted from:

Russo, V.; Herron, J. R.; Ball, Z. T. "Allylcopper Intermediates with N-Heterocyclic Carbene Ligands: Synthesis, Structure, and Catalysis." *Org. Lett.* **2011**, 12, 220

### 4.1 Introduction

The generation of functionalized organometallic reagents is of great value for the synthesis of complex target structures. In one approach to this problem, we have initiated a program to develop and study functional-group tolerant methods for the generation of organocopper species. Copper reagents are generally produced from organomagnesium or other highly reactive organometallics, by selective metalation of organohalides,<sup>1</sup> or through direct metalation with strongly basic reagents<sup>2</sup> (Chapter 1). Important efforts have been made to develop selective cupration strategies, including from stable organoboron<sup>3,4</sup> and organostannane<sup>5</sup> precursors. However, there are significant potential benefits to the use of organosilanes as potentially cheap, stable, and environmentally benign direct precursors to functionalized organocopper reagents

(Chapter 2). The use of fluoride to activate organosilanes is well established, but this approach to the synthesis of reactive organometallics, and to organocopper reagents in particular, is limited by the poor availability of soluble, anhydrous fluoride sources,<sup>6</sup> the instability of copper(I) fluoride toward disproportionation,<sup>7</sup> and the relatively inert carbon-silicon bond. The intermediacy of organocopper species has been inferred in reactions of highly strained silanes<sup>8</sup> and of those activated by intramolecular alkoxides.<sup>9,10</sup> A few reports demonstrating copper catalysts for organosilane dimerization,<sup>11</sup> for coupling of alkynylsilanes,<sup>12</sup> or for nucleophilic addition of organosilanes have appeared,<sup>13</sup> primarily with more easily transferable allylsilane nucleophiles.<sup>14,15</sup> The intermediacy of organocopper species can be inferred in these reactions on the basis of kinetics, NMR, and enantioselection observations,<sup>13,16</sup> but it can be difficult to distinguish reactivity of an organocopper intermediate from that from a fluoride-activated silicate<sup>17,18</sup> (section 2.2.2). To our knowledge, direct observation or characterization of silicon-to-copper transmetalation has not been observed with simple sp<sup>2</sup>- or sp<sup>3</sup>-organosilanes prior to the time this work was conducted.

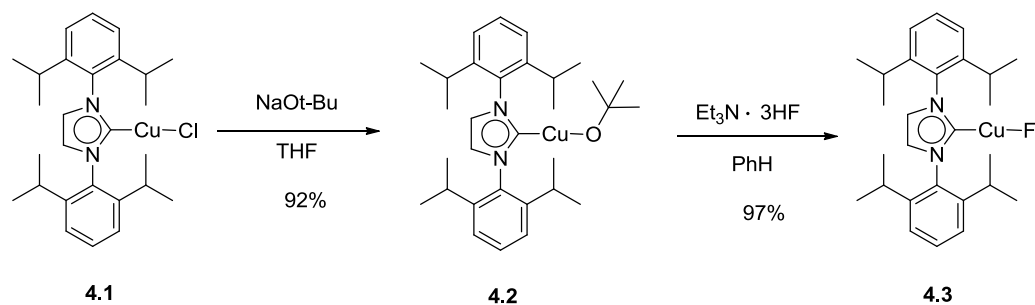
## 4.2 Synthesis of (NHC)CuF complex (4.3)

The first copper(I) fluoride complex, (Ph<sub>3</sub>P)<sub>3</sub>CuF, isolated as ethanol or methanol adducts, was prepared by reaction of aqueous HF with Cu<sub>2</sub>O in the presence of triphenylphosphine in alcoholic solvent.<sup>7,19,20</sup> This complex has found use as a precatalyst for several transformations, notably the aldol reaction of silyl ketene acetals with ketones.<sup>13,21</sup> The only other structurally characterized copper(I) fluoride complex (without employing NHC ligands) was prepared by abstraction of fluoride from the PF<sub>6</sub><sup>-</sup> counter ion of a dicationic diphosphenomethane copper(I) dimer to give a trigonal planar μ<sub>3</sub>-fluorido complex.<sup>22</sup> We require

a stable copper fluoride complex that is free of protic solvents in order to generate stable organocopper species from transmetalation with organosilanes.

To surmount the difficulties associated with copper(I) fluoride complexes (section 4.1), we employ a N-heterocyclic carbene ligand for copper<sup>23-31</sup> to stabilize the copper(I) fluoride and to afford solubility in anhydrous, aprotic solvents. Specifically, we employ the fluoride complex (IPr)CuF (**4.3**) (IPr = 1,3-bis(2',6'-diisopropylphenyl)imidazol-2-ylidene) available upon treatment of (IPr)Cu(O*t*-Bu) (**4.2**) with Et<sub>3</sub>N·3HF in anhydrous benzene, followed by filtration of the product<sup>32</sup> (Scheme 1). Uniquely, (IPr)CuF (**4.3**) is a monomeric, anhydrous copper(I) fluoride complex soluble in ethereal solvents.

#### Scheme 1. Synthesis of (IPr)CuF

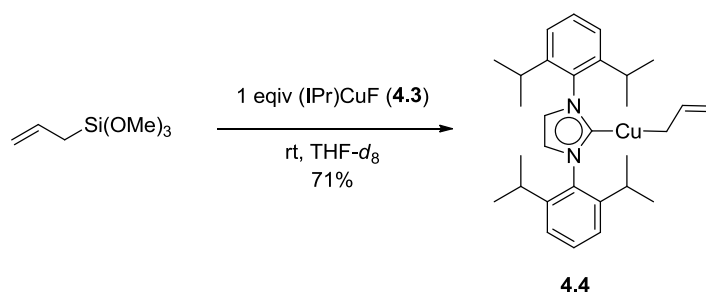


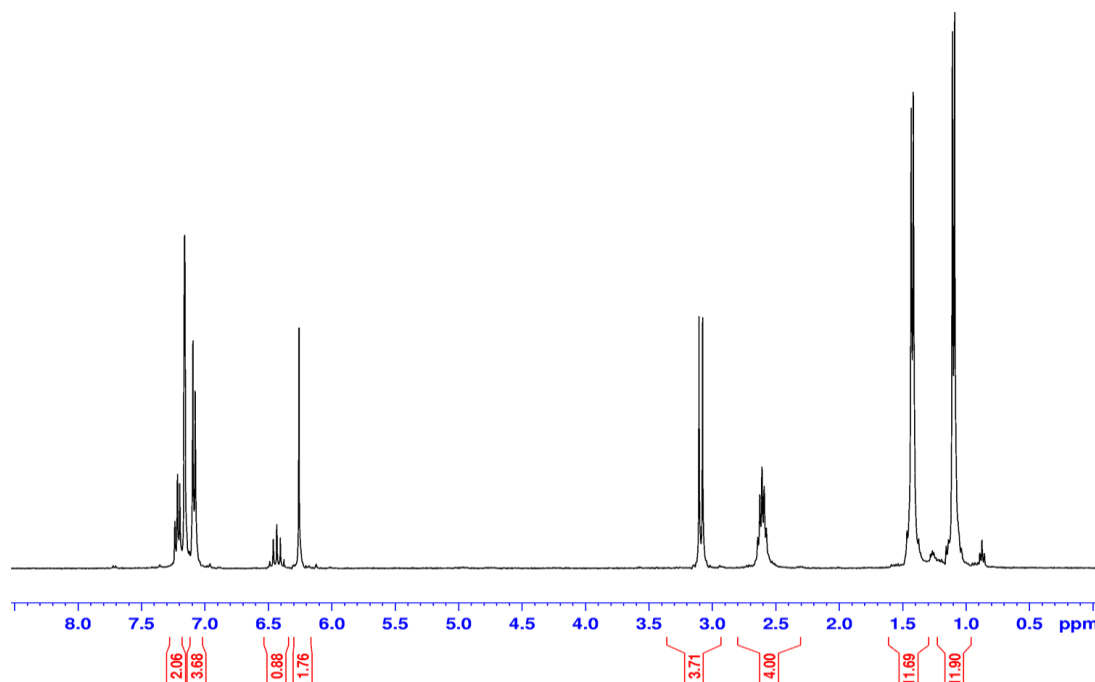
#### 4.3 Transmetalation with allyltrimethoxysilane

The reaction of allyltriethoxysilane with (IPr)CuF (**4.3**) is quite fast (Scheme 2), proceeding to completion in less than 12 min by <sup>1</sup>H NMR analysis of the mixture in THF-*d*<sub>8</sub>.

The product (IPr)Cu(allyl) (**4.4**) can be isolated in analytically pure form by precipitation upon dilution with pentane and cooling. Only two resonances corresponding to the allyl unit are seen in the  $^1\text{H}$  NMR ( $\delta$  6.42, quintet,  $J$  ) 11.1 Hz, 1H); 3.08, d,  $J$  ) 11.1 Hz, 4H), indicating fast exchange between  $\eta^1$  and  $\eta^3$  coordination modes<sup>33</sup> (Figure 1). Cooling a THF- $d_8$  solution of the product allylcopper resulted in significant broadening of the resonances corresponding to the allyl moiety, but no static structure was observed upon cooling to -90 °C.

**Scheme 2. Synthesis of (IPr)Cu(allyl)**

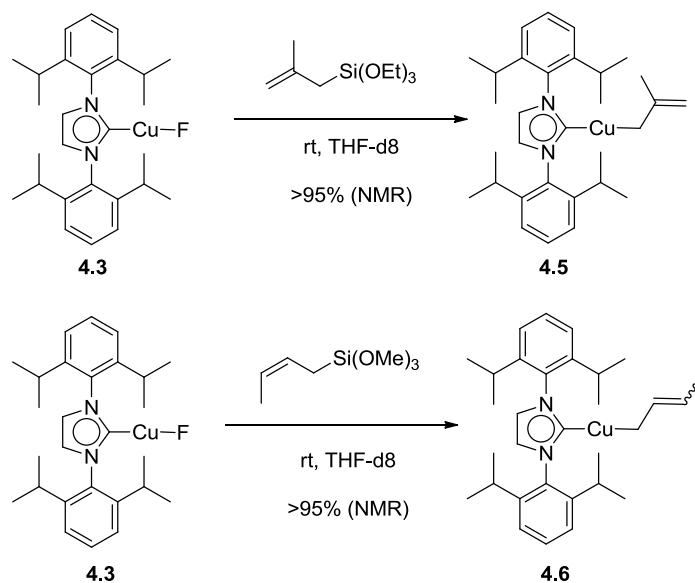


**Figure 1.**  $^1\text{H}$  NMR of (IPr)Cu(allyl), **4.4**

The NMR spectrum of the 2-methallylcopper complex **4.5** is also consistent with fast exchange between  $\eta^1$  and  $\eta^3$  coordination modes (Scheme 3), exhibiting two singlet resonances at  $\delta$  2.14 (4H) and  $\delta$  1.09 (3H) ppm. On the basis of subsequent X-ray structural data, it is likely that the  $\eta^1$  structure is the lower-energy isomer in solution. A previous NMR study of allylic cuprates reported data consistent with an  $\eta^1$  complex,<sup>34</sup> rather than the dynamic structures observed here with neutral allylcopper species. Finally, the crotylsilane reagent reacts with (IPr)CuF, affording an organocopper complex **4.6** with a  $^1\text{H}$  NMR spectrum containing four peaks for an allylcopper complex at  $\delta$  5.39 (1H), 3.93 (1H), 0.99 (3H), and 0.59 (2H) ppm. Although stable for hours in solution (THF) at room temperature, the substituted complexes **4.5** and **4.6** are significantly less stable than the parent allyl complex **4.4**, and we have been unable to isolate complexes **4.5** or **4.6** in reasonable yield. However, it is possible to grow single crystals of the complexes **4.4** and **4.5** suitable for X-ray diffraction by diffusional recrystallization in THF/pentane at  $-35^\circ\text{C}$ . The X-ray

structures of compounds **4.4** and **4.5** (Figure 2) show that both complexes crystallize in the  $\eta^1$  coordination mode, without significant interaction between the metal and the  $\pi$  system.

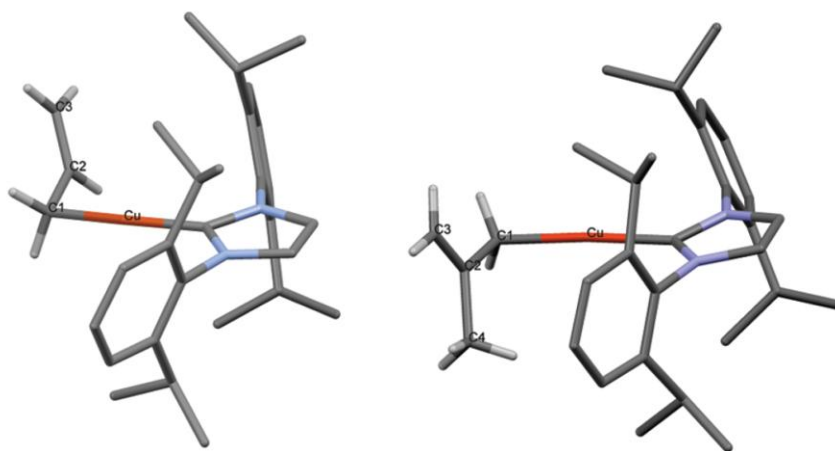
### Scheme 3. Synthesis of allylcopper species



The crystal structures of **4.4** and **4.5** exhibit dihedral angles for the allyl ligand (Cu-C1-C2dC3) of 108.0° and 103.0°, respectively (Figure 2). These dihedral angles are consistent with hyperconjugative interactions for ( $\eta^1$ -allyl)palladium complexes with pincer ligands that have been shown to catalyze allylation of allylstannanes by a transmetalation mechanism.<sup>35</sup> In addition, the allyl units have C2=C3 bond lengths of 1.306 and 1.278 Å, similar to that expected for a free double bond. The lack of intermolecular interactions in the solid state provides evidence that these allylcopper species are likely monomeric in solution as well, in contrast to many organocuprates<sup>36,37</sup> (Chapter 1).



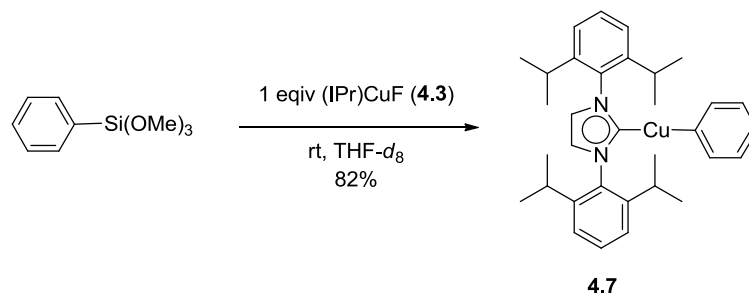
**Figure 2. X-ray structure of complexes 4.4 and 4.5**



#### 4.4 Synthesis of arylcopper species

Treatment of (IPr)CuF in THF-*d*8 with phenyltriethoxysilane induced clean transmetalation within 1 h at rt, affording the product (IPr)CuPh (Table 1, entry 1). Gratifyingly, the product organometallic could be isolated in analytically pure form by precipitation upon dilution with pentane and cooling.

#### Scheme 4. Synthesis of (IPr)Cu(Ph)



We set out to explore the generality and functional group tolerance of our approach to organocopper reagents (Table 1). Although we have focused on trialkoxysilanes, (dialkyl)monoalkoxysilyl groups are much more stable to silica chromatography and to hydrolysis generally, and so we were pleased to find that phenyldimethylethoxysilane (Table 1, entry 2) undergoes efficient transmetalation as well, with a rate only slightly slower than the trialkoxysilane (entry 1). Despite the bulk of the IPr ligand, ortho-substituted arylcopper reagents are readily formed (entries 3-4), and both electron-rich and electron-poor arylsilanes are tolerated (entries 5-8). Unfortunately pyridalsilanes (entries 9-10) only provide decomposition products. The organocopper species that do not react to completion cannot (in our hands) be isolated from the other copper reagents present in the reaction mixture.

**Table 1. Synthesis of functionalized organocopper compounds**

$$\text{R-SiR}'_3 \xrightarrow[\text{R}'_3\text{SiF}]{(\text{IPr})\text{CuF, THF, rt}} (\text{IPr})\text{Cu-R}$$

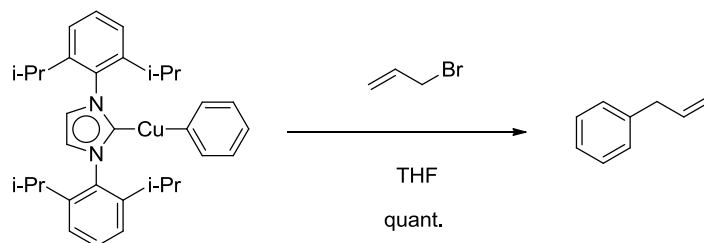
entry	silane	number	yield <sup>a,b</sup>
1		<b>4.7</b>	82 (>95%)
2		<b>4.7</b>	(>95%)
3		<b>4.8</b>	71 (>95%)
4		<b>4.9</b>	88 (>95%)
5		<b>4.10</b>	73 (>95%)
6		<b>4.11</b>	(90%)
7		<b>4.12</b>	(>95%)
8		<b>4.13</b>	65 (>95%)
9		-	0
10		-	0

<sup>a</sup>All reactions were performed at room temperature in THF unless otherwise indicated. Yields indicate isolated yields of analytically pure material. <sup>b</sup>Yields in parenthesis are NMR yields.

## 4.5 Reactivity of arylcopper species

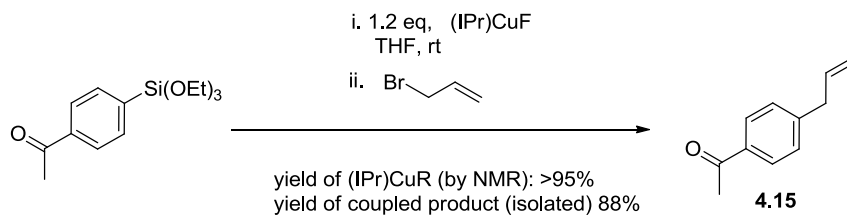
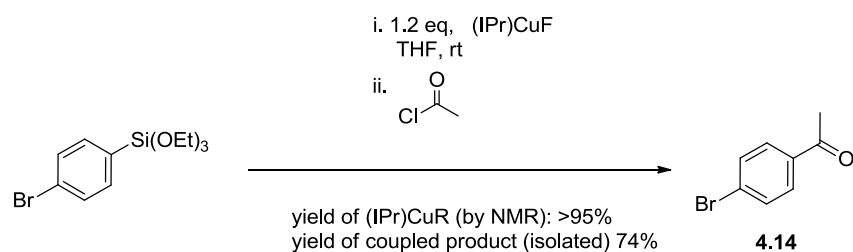
Having established a general preparative method for polyfunctionalized aromatic copper compounds, we next examined the reactivity of arylcopper compounds. Pure phenylcopper **4.7** reacts cleanly with allyl bromide, affording allylbenzene (quant yield by NMR).

### Scheme 5. Reaction with (IPr)Cu(Ph) and allyl bromide

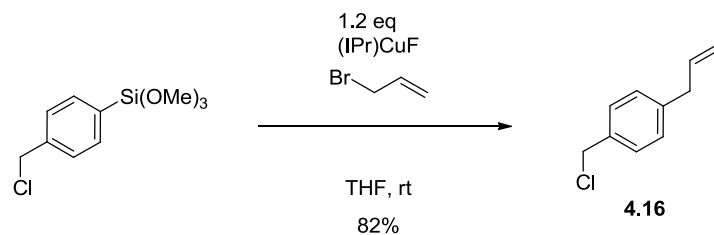


Other organocopper reagents, including bromide **4.13** have been generated in quantitative yield (NMR) by treating the arylsilane with 1.2 equiv of (IPr)CuF (**4.3**). Treatment of this crude mixture with acetyl chloride allowed isolation of the product ketone **4.15** (Scheme 5). Similarly, the acetophenone derivative affords a stable organocopper species (**4.12**) observed by  $^1\text{H}$  NMR, and the ketone **4.16** was readily isolated following treatment with allyl bromide (Scheme 5). The ability to form stable organocopper reagents from substrates bearing a methyl ketone group with acidic  $\alpha$ -hydrogen atoms in this example is noteworthy. Finally, the reaction of a benzylic chloride substrate with (IPr)CuF affords an organocopper species, observable by  $^1\text{H}$  NMR, which is significantly less stable than others in this study, and which decomposes at a rate competitive with its formation (Scheme 6). In this case, performing the transmetalation in the presence of allyl bromide allowed clean coupling to afford the chloride **4.17**.

### Scheme 6. Reactivity of arylcopper compounds



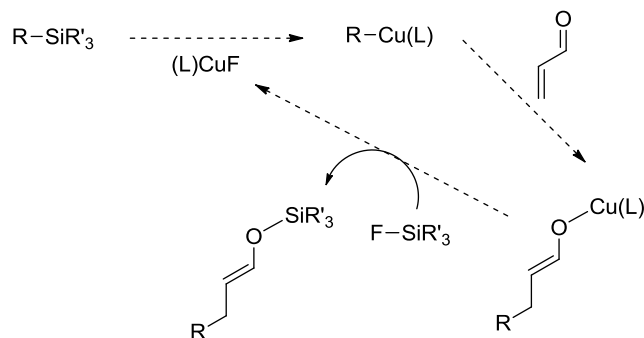
### Scheme 7. Generation of organocopper species bearing a benzylic chloride substituent



#### 4.6 The question of turnover

An important future goal of the transmetalation procedure outlined here is the development of a bond-forming process of organosilanes using catalytic quantities of (NHC)CuF complexes. Mechanistically, we would hold the electrophile responsible for regenerating an active copper species. Addition products providing fluoride leaving groups, copper alkoxides, or copper enolates would potentially provide access to such a system (Scheme 7).

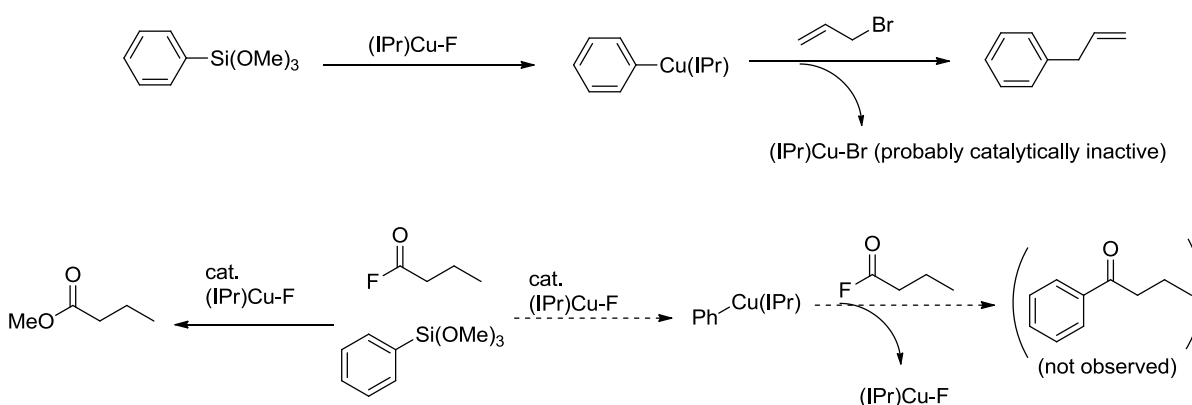
**Scheme 8. The question of turnover**



Initial attempts in this direction using fluoride as a leaving group were unsuccessful for carbon-carbon bond formation. The reaction with 5 mol % (IPr)CuF, phenyltrimethoxysilane, and an acyl fluoride resulted in the undesired carbon-oxygen formation (Scheme 8). However, this result led us to believe that transmetalation with the organosilane accesses both copper alkoxide and copper phenyl species. These two species may simply have different reactivities

toward electrophiles. With this result in mind, we believe that copper alkoxides resulting from 1,2-addition to aldehydes would be catalytically competent species.

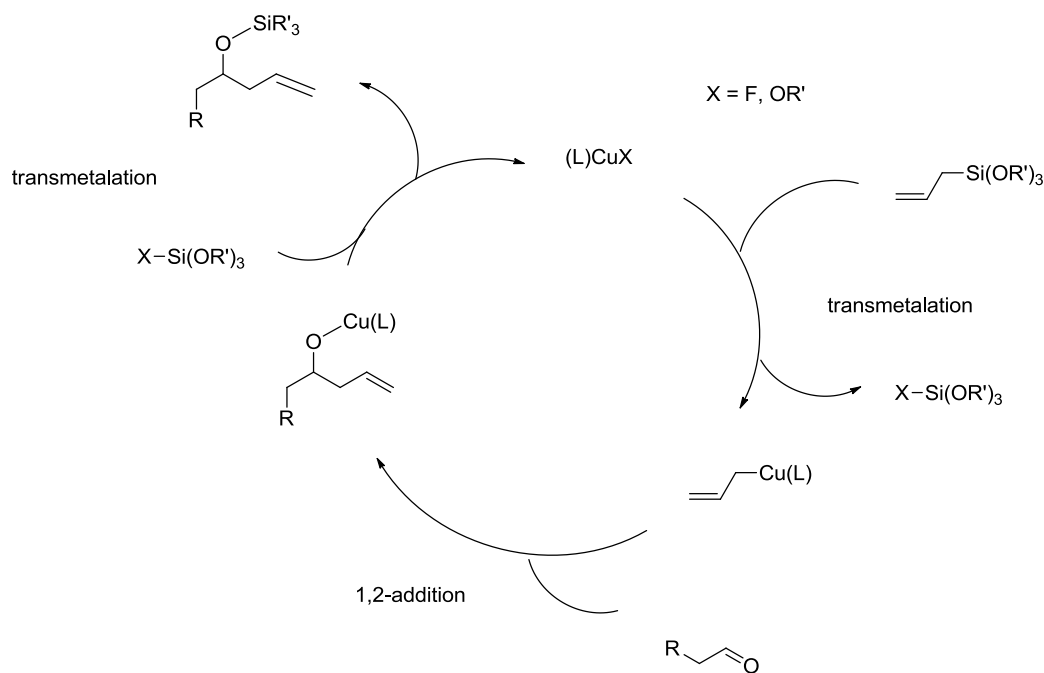
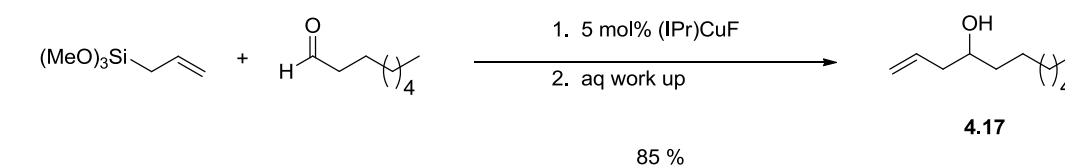
#### Scheme 9. C-O bond formation



#### 4.7 Catalytic aldehyde allylation with (IPr)CuF

We found that (IPr)CuF catalyzes the allylation of octanal in good yield (Scheme 9). This result indicates that (IPr)Cu-alkoxides, such as that formed after 1,2-addition of an allylcopper intermediate, are catalytically competent to continue on the catalytic cycle and opens opportunities for the development of other catalytic and potentially stereocontrolled processes. The (IPr)CuF-catalyzed allylation is a part of the small class of a catalytic allylation reactions proceeding by a transmetalation mechanism.<sup>38,39</sup>

**Scheme 10. Catalytic aldehyde allylation with (IPr)CuF**



After discovering that (IPr)CuF (**4.3**) catalyzes the allylation of allyltrimethoxysilane with octanal, a preliminary screening of solvents was conducted. Tetrahydrofuran was found to provide the highest yields. Unfortunately, the efficiency of catalytic reactivity with this initial

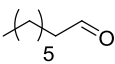
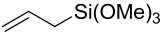
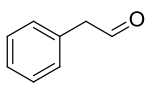
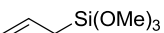
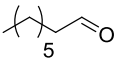
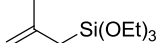

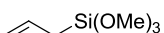
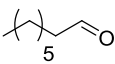
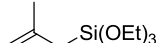
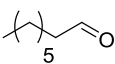
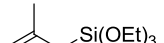
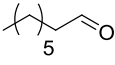
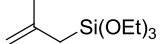
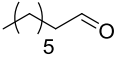
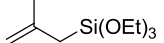
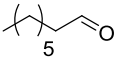
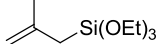
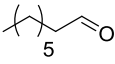
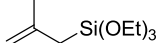
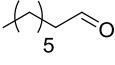
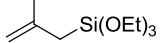


result was quite limited: extension of the reaction to other aldehydes or to the substituted allylsilanes was unproductive (Table 2, entries 3, 4). The lower reactivity of methallyl silanes is in contrast to the inherent nucleophilicity of more electron-rich methallyl species relative to unsubstituted allylmetals. We examined additives that might improve the efficiency and generality of the catalytic process. Because stoichiometric examinations had convinced us that transmetalation is a fast process with allylsiloxanes, we examined a variety of metal salts with the hope that Lewis acids might facilitate the C-C bond-forming step (Table 2). In a screen of Lewis acid additives, lithium salts provided no benefit, but some lanthanide triflate salts did allow low yields of allylation product (entries 8-10). In a search for Lewis acids that would be soluble in aprotic solvent and would not prevent turnover of the copper catalyst, we examined the use of trifluorosilanes.<sup>40</sup> Remarkably, a great improvement in reactivity is obtained when using octyltrifluorosilane as an additive. This result has proven general, allowing clean catalytic reactivity with substrates that are unproductive without the trifluorosilane.

The role of a trifluorosilane additive in the catalytic process remains unclear. After the discovery of this additive, an NMR experiment demonstrated that allylcopper complexes formed in situ do react smoothly with aldehydes within minutes at room temperature. Furthermore, additional allylsilane can be added after 1,2-addition, regenerating the allylcopper complex, all without the need for a trifluorosilane additive. Thus all steps on the catalytic cycle appear kinetically competent, but the catalytic system does not function in the absence of additive. This may point to a role of trifluorosilane additives in increasing turnover rate by increasing fluoride concentration, in thwarting catalyst-kill events, or in allowing an inactive catalyst form to be reintroduced in the catalytic cycle.

We have verified that trifluorooctylsilane alone does not catalyze the reactions. We have also considered the possibility that the trifluorooctylsilane might serve as a dehydrating agent or alternatively as a source of water, but rigorous exclusion of water or addition of small quantities of water both fail to produce a beneficial result.

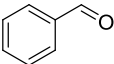
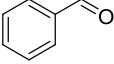
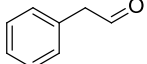
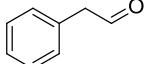


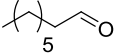
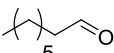
**Table 2. Allylations of aldehydes with 5 mol % (IPr)CuF**

$  \begin{array}{c}  \text{R} \text{---} \text{C}(=\text{O}) \text{H} + \text{CH}_2=\text{CH}-\text{R}'-\text{Si}(\text{OR}'')_3 \xrightarrow[\text{THF, rt}]{\substack{5 \text{ mol } \% \text{ 4.3} \\ 10 \text{ mol } \% \text{ additive}}} \text{R}-\text{CH}(\text{OH})-\text{CH}(\text{R}')-\text{CH}=\text{CH}_2  \end{array}  $				
entry	substrate	silane	additive	yield (%) <sup>b,c</sup>
1			-	88
2			-	42
3			-	-
4			-	-
5			LiBF <sub>4</sub>	-
6			LiPF <sub>6</sub>	-
7			LiOTf	-
8			In(OTf) <sub>3</sub>	17
9			La(OTf) <sub>3</sub>	13
10			Eu(OTf) <sub>3</sub>	9
11			( <i>n</i> -octyl)SiF <sub>3</sub>	72

<sup>a</sup> The reaction time was 48 h. <sup>b</sup> Isolated yield after column chromatography. <sup>c</sup> Yields were determined by NMR spectroscopy, using 1,4-dimethoxybenzene as an internal standard (entries 5-9).

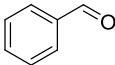
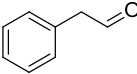

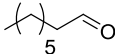
Using the silicon trifluoride additive to enhance the reactivity of the allylcopper species, we studied the reaction of five different aldehydes with allyltrimethoxysilane, (2-methylallyl)triethoxysilane, and (Z)-crotyltrimethoxysilane (Tables 3 and 4 and Scheme 2). The reaction succeeds even with the readily enolized substrate phenylacetaldehyde (Table 3, entries 3, 4; Table 4, entry 2). With a (Z)-crotylsilane, modest preference for products with the 1,2-anti stereochemistry is observed. This stereochemical outcome is consistent with an open transition state. The terminal olefin products of S<sub>E</sub>2' addition are observed exclusively, despite the conformational lability of the allylcopper intermediate.

**Table 3. Allylations of aldehydes with trifluorosilane additive**

$\text{R}-\text{CHO} + \text{CH}_2=\text{CH}-\text{CH}(\text{R}')-\text{Si}(\text{OR}'')_3 \xrightarrow[\text{THF, rt}]{\substack{5 \text{ mol } \% \text{ 4.3} \\ 10 \text{ mol } \% (n\text{-octyl})\text{SiF}_4}} \text{R}-\text{CH}(\text{OH})-\text{CH}_2-\text{CH}(\text{R}')-\text{CH}=\text{CH}_2$				
entry	aldehyde	R' <sup>a</sup>	number	yield (%) <sup>b</sup>
1		H	<b>4.18</b>	81
2		Me	<b>4.19</b> <b>4.20</b>	75
3		H	<b>4.21</b>	73
4		Me	<b>4.22</b>	72
5		H	<b>4.23</b>	56
6		Me	<b>4.24</b>	65
7		H	<b>4.17</b>	88
8		Me	<b>4.25</b>	72

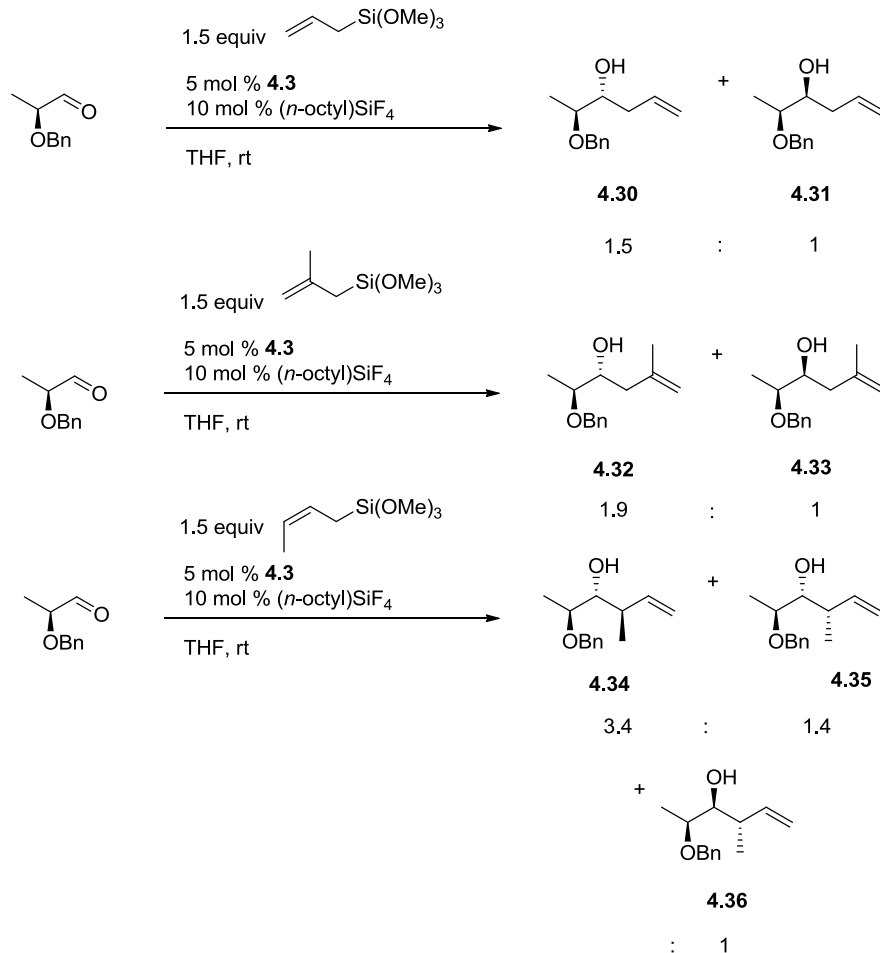
<sup>a</sup> When R' = Me, the silane is -Si(OEt)<sub>3</sub>. <sup>b</sup> Isolated yield after column chromatography

**Table 4. Diastereoselective allylation of aldehyde with crotyltrimethoxysilane**

$  \begin{array}{c}  \text{R}-\text{CHO} \xrightarrow[\text{THF, rt}]{\begin{array}{l} 1.5 \text{ equiv } \text{CH}_3\text{CH=CHSi(OMe)}_3 \\ 5 \text{ mol } \% \text{ 4.3} \\ 10 \text{ mol } \% (n\text{-octyl})\text{SiF}_4 \end{array}} \text{R}-\text{CH(OH)}-\text{CH=CH}_2 + \text{R}-\text{CH(OH)}-\text{CH}_2\text{CH=CH}_2  \end{array}  $				
entry	aldehyde	number	yield (%) <sup>a</sup>	anti/syn <sup>b</sup>
1		<b>4.26</b>	78	2:1
2		<b>4.27</b>	66	2.5:1
3		<b>4.28</b>	61	4:1
4		<b>4.29</b>	79	3:1

<sup>a</sup> Isolated yields of pure compounds. <sup>b</sup> The syn/anti ratio was determined by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

Diastereoselectivity was unaltered when the (*E*)-crotyltrimethoxysilane was used, consistent with our observation that the allylcopper intermediate participates in fast  $\eta^1$ - $\eta^3$  interconversion.

**Scheme 11. Allylations of aldehydes with 5 mol % (IPr)CuF**

A chiral aldehyde, 2-benzyloxypropionaldehyde, was also examined (Scheme 10). Efficient allylation does occur with this substrate, and consistent with the low Lewis acidity of the organocopper intermediate, the major isomer is that of nonchelate, Felkin-Ahn selectivity.<sup>41</sup> However, poor selectivities are observed with all three allylic nucleophiles. The reaction between 2-benzyloxypropanal and crotyltrimethoxysilane generates a mixture of four diastereomers, of which only three were observed in appreciable yield.

## 4.8 Concluding Remarks

Organometallic (NHC)-copper complexes are important as presumed intermediates in a number of synthetically useful catalytic reactions. However, there are few general methods available for the synthesis of organocopper-NHC complexes,<sup>42</sup> and many of these require inconvenient or functional-group intolerant organometallic precursors.<sup>28,32</sup> (NHC)copper species serve as increasingly valuable catalysts for reactions assumed to involve organocopper intermediates, and we believe that the method described here will allow a more thorough investigation of the mechanism and selectivity questions in these processes. Copper(I) fluoride complexes have seen limited use in synthesis owing to the lack of soluble, anhydrous complexes available without the presence of protic solvent molecules, and the work here demonstrates that new, well defined, anhydrous copper(I) fluoride complexes enable new reactivity and catalysis.

We have demonstrated a synthetic approach to NHCallylcopper complexes and report the first crystal structures of allylcopper species. The complex (IPr)CuF can be employed for the catalytic allylation of aldehydes with allylsilanes by a transmetalation mechanism, and a trifluorosilane additive was discovered to significantly facilitate this process. We intend to use this study as a launching pad for the development of other catalytic reactions of allylcopper intermediates and to extend this study to enantioselective allylation reactions using chiral ligands.

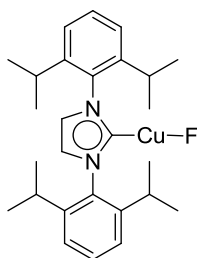
## 4.9 Experimental

### General information

All synthetic manipulations were carried out using standard Schlenk techniques under a nitrogen atmosphere or in a nitrogen-atmosphere glovebox. All reactions were carried out in flame-or oven-dried glassware unless otherwise indicated. THF, ether, and benzene were distilled from sodium benzophenone ketyl under nitrogen. DMF and Et<sub>3</sub>N were distilled from calcium hydride under nitrogen. Anhydrous NMP was purchased from Aldrich and sparged vigorously with nitrogen for 30 min prior to first use. Pentane was sparged with nitrogen and stored in a glovebox. All other solvents were reagent grade. NMR solvents were dried and degassed as follows: C<sub>6</sub>D<sub>6</sub> (Cambridge Isotope Laboratories) over sodium/benzophenone, CD<sub>2</sub>Cl<sub>2</sub> (Cambridge Isotope Laboratories) over P<sub>2</sub>O<sub>5</sub>, and THF-*d*<sub>8</sub> (Cambridge Isotope Laboratories) over sodium/benzophenone. All NMR solvents were degassed with three freeze-pump-thaw cycles and vacuum-transferred prior to use. Flash chromatography was performed with 40-63 μm particle size silica gel. NMR data were acquired with Bruker Avance 400 MHz or Bruker Avance 500 MHz instruments. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded relative to residual solvent. <sup>19</sup>F NMR spectra were recorded on a Bruker Avance 500 MHz instrument, with shifts relative to a CFCl<sub>3</sub> standard. The following chemicals were purchased and used as received: 2,6-diisopropylaniline (Acros), glyoxal (40 wt. % solution in water Aldrich), formic acid (88% Fisher Scientific), paraformaldehyde (Acros), triethylamine tris(hydrofluoride) (Acros), magnesium (Acros), tetraethyl orthosilicate (Aldrich), [(cod)<sub>2</sub>Rh]BF<sub>4</sub> (Strem), triethoxysilane (Gelest), tetraethylammonium iodide (Aldrich), Pd(dba)<sub>2</sub> (Strem), P(*t*-Bu)<sub>2</sub>(*o*-biphenyl) (Strem), *N,N*-diisopropylethylamine (Aldrich), benzaldehyde (Acros), Phenylacetaldehyde (Acros), isobutyraldehyde (Acros), octanal (Acros). Copper(I) chloride (Strem), sodium *tert*-butoxide (Acros), lithium hexafluorophosphate (Acros), lithium triflate (Aldrich), scandium triflate (Strem), indium triflate (Strem), ytterbium triflate (Strem), lanthanum triflate (Strem), and

europium triflate (Strem) were used as received, stored, and weighed in a glovebox. 1,4-Bis(2,6-diisopropylphenyl)diazabutadiene,<sup>43</sup> IPr·HCl,<sup>44</sup> (IPr)CuCl,<sup>26</sup> (IPr)CuOt-Bu,<sup>25</sup> 2-(triethoxysilyl)anisole,<sup>45</sup> 2-(triethoxysilyl)toluene,<sup>45</sup> 4-bromo(triethoxysilyl)benzene,<sup>46</sup> and 4-(triethoxysilyl)acetophenone,<sup>47</sup> methyl 4-(triethoxysilyl)benzoate,<sup>47</sup> 5-triethoxysilyl-(1-methyl-indole),<sup>45</sup> and 4-triethoxysilyl-(3-ethoxy-3-oxopropyl)phenyl<sup>47</sup> were synthesized according to literature protocols. We have not obtained satisfactory elemental analysis for our organocopper products; previous reports indicate that satisfactory elemental analysis cannot be obtained for this class of compounds.

### (IPr)CuF, 4.3

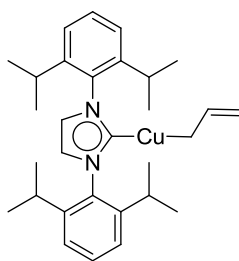


In a glovebox, (IPr)CuOt-Bu (1.22 g, 2.34 mmol) and benzene (21 mL) were added to a round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with a rubber septum and removed from the glovebox. Triethylamine tris(hydrofluoride) (0.120 mL, 0.74 mmol) was added via syringe. The resulting white suspension was stirred for 6 h and the solvent was removed via reduced pressure. In the glovebox, the white solid was suspended in pentane (6 mL), filtered, and washed with pentane (6 mL) to afford the title compound (0.97 g, 89%). Data is consistent with published spectral data.<sup>32</sup>



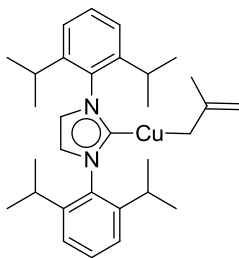
$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  7.54 (t,  $J$  = 7.8 Hz, 4 H), 7.36 (d,  $J$  = 7.9 Hz, 4 H), 7.19 (s, 2 H), 2.57 (sep.,  $J$  = 6.9 Hz, 4 H), 1.31 (d,  $J$  = 7.0 Hz, 12 H), 1.24 (d,  $J$  = 7.0 Hz, 12 H).  $^{19}\text{F}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  -240.7.  $^{13}\text{C}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  180.7, 146.6, 135.2, 130.9, 124.7, 124.0, 29.2, 25.0, 24.1

**(IPr)Cu(allyl) (4.4)**



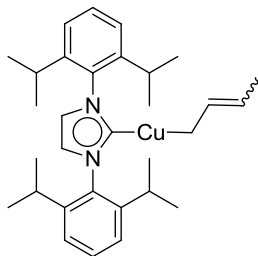
In a glovebox, (IPr)CuF (30 mg, 0.064 mmol) and tetrahydrofuran (1.0 mL) were added to a 25 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with rubber septum and removed from the glovebox. Allyltrimethoxysilane (0.050 mL, 0.282 mmol) was added via syringe. The resulting tan solution was stirred for 15 min. In the glovebox, pentane (20 mL) was added and the solution was placed in a liquid-nitrogen-chilled cold well for 15 min. The resulting white suspension was filtered and washed with pentane (20 mL) to afford the title compound (19 mg, 60%).

$^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  (ppm) 7.22 (t,  $J$  = 7.6 Hz, 2 H), 7.08 (d,  $J$  = 7.68 Hz, 4 H), 6.43 (quin,  $J$  = 11.1 Hz, 1 H), 6.26 (s, 2 H), 3.09 (d,  $J$  = 11.1 Hz, 4 H), 2.61 (sep,  $J$  = 6.9 Hz, 4 H), 1.42 (d,  $J$  = 6.9 Hz, 12 H), 1.1 (d,  $J$  = 6.9 Hz, 12 H).  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta$  185.3, 146.9, 145.6, 135.2, 130.3, 124.0, 121.9, 59.0, 28.8, 24.8, 23.6.

**(IPr)copper(I) 1-methallyl, 4.5**

In the glove box, (IPr)CuF (20.0 mg, 0.042 mmol) was dissolved in THF-*d*<sub>8</sub> (0.50 mL) in an NMR tube. The tube was then sealed with a rubber septum and taken out of the box. (2-methyl-2-propenyl)triethoxysilane (9.3 mg, 0.042 mmol) was added via syringe to the solution in the NMR tube and a spectrum (400 MHz) was recorded after 10 min. Two singlet resonances, at 2.14 (4 H) and 1.09 (3 H) ppm, were observed, corresponding to the allylcopper species in fast equilibrium between the  $\eta^1$  and  $\eta^3$  coordination modes.

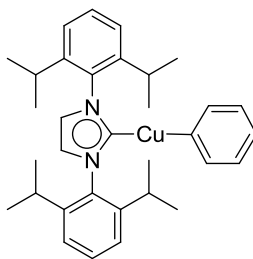
**(IPr)copper(I) 1-methallyl, 4.6**



In the glove box, (IPr)CuF (20.0 mg, 0.042 mmol) was dissolved in THF- $d_8$  (0.50 mL) in an NMR tube. The tube was then sealed with a rubber septum and taken out of the box.

Crotyltrimethoxysilane (7.5 mg, 0.042 mmol) was added via syringe to the solution in the NMR tube and a spectrum (400 MHz) was recorded after 10 min. The spectrum showed for resonances at 5.39, 3.93, 0.99 and 0.59 ppm, corresponding to the allylcopper species.

#### (IPr)CuPh, 4.7

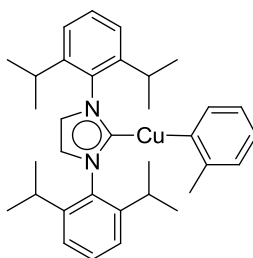


In a glovebox, (IPr)CuF (363 mg, 0.774 mmol) and ether (15 mL) were added to a 100 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with a rubber septum and removed from the glovebox. Trimethoxyphenylsilane (0.365 mL, 1.95 mmol) was added via syringe. The resulting tan solution was stirred for 2 h. In the glovebox, pentane (60 mL) was

added and the mixture cooled in a liquid-nitrogen-chilled cold well for 15 min. The resulting white suspension was filtered and washed with pentane (40 mL) to afford the title compound (0.335 g, 82%). Data is consistent with published spectral data.<sup>28,48</sup>

<sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  7.65 (m, 2H), 7.23 (t,  $J$  = 7.6 Hz, 4 H), 7.13 (m, 1 H), 7.08 (d,  $J$  = 7.6 Hz, 4 H), 6.28 (s, 2 H), 2.64 (sep.,  $J$  = 6.8 Hz, 4 H), 1.41 (d,  $J$  = 6.8 Hz, 12 H), 1.10 (d,  $J$  = 6.8 Hz, 12 H). <sup>13</sup>C NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>):  $\delta$  186.1, 166.1, 146.2, 141.1, 135.5, 130.8, 126.6, 124.6, 124.5, 122.6, 29.3, 25.5, 24.0.

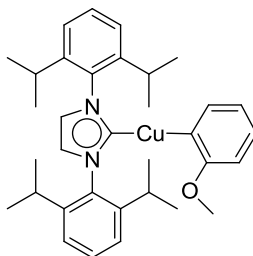
**(IPr)Cu(2-methylphenyl), 4.8**



In a glovebox, (IPr)CuF (47 mg, 0.10 mmol) and ether (0.50 mL) were added to a 25 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with a rubber septum and removed from the glovebox. 2-(triethoxysilyl)toluene (0.070 mL, 0.27 mmol) was added via syringe. The resulting tan solution was stirred for 4 h. In the glovebox, pentane (10 mL) was added and the mixture cooled in a liquid-nitrogen-chilled cold well for 15 min. The resulting white suspension was filtered and washed with pentane (20 mL) to afford the title compound (38 mg, 71%).

$^1\text{H}$  NMR ( $\text{CD}_2\text{Cl}_2$ )  $\delta$  (ppm): 7.53 (t,  $J = 7.7$  Hz, 2H, 0.0117 ppm), 7.34 (d,  $J = 7.7$  Hz, 4H), 7.06 (s, 2H), 6.90 (d,  $J = 6.8$  Hz, 1H), 6.75-6.69 (m, 2H), 6.65 (d,  $J = 6.8$  Hz, 1H), 2.68 (sep.,  $J = 6.8$  Hz, 4H), 1.84 (s, 3H), 1.31 (d,  $J = 6.8$  Hz, 12H), 1.25 (d,  $J = 6.8$  Hz, 12H).  $^{13}\text{C}$  NMR ( $\text{CD}_2\text{Cl}_2$ ):  $\delta$  185.3, 167.5, 147.7, 146.5, 140.2, 135.6, 130.6, 125.9, 124.7, 123.9, 123.3, 122.7, 29.3, 28.5, 25.1, 24.2.

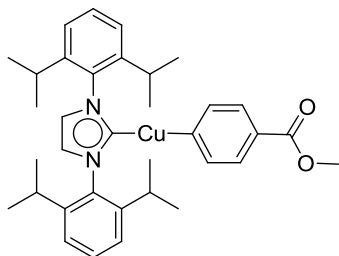
**(IPr)Cu(2-methoxyphenyl) (2d)**



In a glovebox, (IPr)CuF (112 mg, 0.239 mmol) and ether (6 mL) were added to a 100 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with rubber septum and removed from the glovebox. 2-(Triethoxysilyl)anisole (0.120 mL, 0.448 mmol) was added via syringe. The resulting tan solution was stirred for 1 h. In the glovebox, pentane (60 mL) was added and the solution was placed in a liquid-nitrogenchilled cold well for 15 min. The resulting white suspension was filtered and washed with pentane (40 mL) to afford the title compound (0.117 g, 88%).

$^1\text{H}$  NMR (400 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  7.6 (m, 1 H), 7.22 (t,  $J = 7.9$  Hz, 2 H), 7.13 (m, 1 H), 7.07 (d,  $J = 7.9$  Hz, 4 H), 7.01-6.95 (m, 2 H), 6.30 (s, 2 H), 3.44 (s, 3 H), 2.63 (sep.,  $J = 6.9$ ), 1.37 (d,  $J = 6.9$ , 12H), 1.09 (d,  $J = 6.9$ , 12 H).  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta$  185.7, 168.2, 147.7, 145.8, 141.1, 135.3, 130.3, 125.3, 124.1, 54.8, 28.9, 24.8, 23.7.

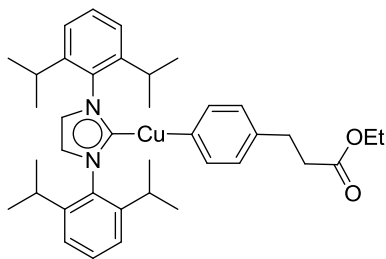
**(IPr)Cu(4-(methoxycarbonyl)phenyl), 4.10**



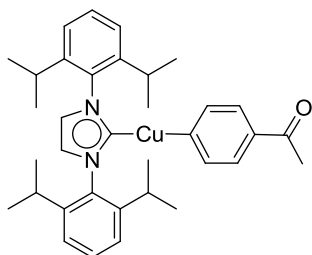
In a glovebox, (IPr)CuF (41 mg, 0.087 mmol) and THF- $d_8$  (0.5 mL) were added to an NMR tube. The tube was then sealed with a rubber septum and removed from the glovebox. Methyl 4-(triethoxysilyl)benzoate (0.040 mL, 0.142 mmol) was added via syringe. The solution was monitored by  $^1\text{H}$  NMR. The reaction was complete in 3.5 h. In the glovebox, the solution was transferred to a round-bottom flask. Pentane (15 mL) was added and the solution was placed in a liquid-nitrogen-chilled cold well for 15 min. The resulting white suspension was filtered, and washed with pentane (20 mL) to afford the title compound (37 mg, 72%).

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_2\text{Cl}_2$ ):  $\delta$  7.51 (t,  $J = 7.8$  Hz, 2 H), 7.42 (m, 2 H), 7.33 (d,  $J = 7.8$  Hz, 4 H), 7.18 (s, 2 H), 7.17-7.14 (m, 2 H), 3.79 (s, 3 H), 2.66 (sep.,  $J = 6.8$  Hz, 4 H), 1.34 (d,  $J = 6.8$  Hz, 12 H), 1.25 (d,  $J = 6.8$  Hz, 12 H).  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ ):  $\delta$  184.0, 175.4, 168.5, 145.9, 139.7, 134.9, 130.2, 125.6, 125.2, 124.0, 123.0, 51.2, 28.8, 24.7, 23.5.

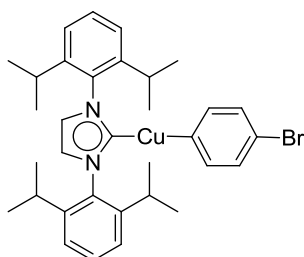
**(IPr)Cu(4-(3-ethoxy-3-oxopropyl)phenyl), 4.11**



In a glovebox, (IPr)CuF (15 mg, 0.0319 mmol) was dissolved in  $\text{THF-}d_8$  (0.45 mL) in an NMR tube. The tube was then sealed with a rubber septum and taken out of the box. 4-(triethoxysilyl)-(3-ethoxy-3-oxopropyl)phenyl (21.4 mg, 0.0628 mmol) was added via syringe to afford the organocopper complex, formed in 90 % yield by NMR analysis (selected resonances  $^1\text{H}$  NMR (400 MHz,  $\text{THF } d_8$ ):  $\delta$  7.46 (t,  $J = 7.8$  Hz, 2H), 7.46 (s, 2H), 7.33 (d,  $J = 7.8$  Hz, 4H), 6.88 (d,  $J = 8.0$  Hz, 2H), 6.52 (d,  $J = 8.0$  Hz, 2H), 4.00 (q,  $J = 7.0$  Hz, 2H), 2.73 (sep.,  $J = 6.9$  Hz, 4H), 2.58 (t,  $J = 7.0$  Hz, 2H), 2.34 (t,  $J = 7.0$  Hz, 2H), 1.36 (d,  $J = 7.0$  Hz, 12H), 1.25 (d,  $J = 7.0$  Hz, 12H), 1.19 (t,  $J = 7.0$  Hz, 3H).

**(IPr)Cu(4-(methylcarbonyl)phenyl), 4.12**

In a glovebox, (IPr)CuF (220 mg, 0.469 mmol) and THF (4.5 mL) were added to a 25 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with rubber septum and removed from the glovebox. 4-(triethoxysilyl)acetophenone (110 mg, 0.391 mmol) was added via syringe to afford the organocopper complex, formed in quantitative yield by NMR analysis (selected resonances  $^1\text{H}$  NMR (400 MHz,  $\text{THF-}d_8$ ):  $\delta$  7.47 (t,  $J = 7.8$  Hz, 2H), 7.35 (d,  $J = 7.8$  Hz, 4H), 7.31 (s, 2H), 7.27 (d,  $J = 8.0$  Hz, 2H), 7.07 (d,  $J = 8.0$  Hz, 2H), 2.72 (sep.,  $J = 6.9$  Hz, 4H), 2.27 (s, 3H), 1.35 (d,  $J = 6.9$  Hz, 12H), 1.26 (d,  $J = 6.9$  Hz, 12H)).

**(IPr)Cu(4-bromophenyl), 4.13**

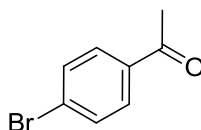
In a glovebox, (IPr)CuF (37 mg, 0.079 mmol) and ether (0.50 mL) were added to a 25



mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with a rubber septum and removed from the glovebox. 4-Bromo(triethoxysilyl)benzene (0.050 mL, 1.32 mmol) was added via syringe. The resulting tan solution was stirred for 4 h. In the glovebox, pentane (10 mL) was added and the mixture cooled in a liquid-nitrogenchilled cold well for 15 min. The resulting white suspension was filtered and washed with pentane (20 mL) to afford the title compound (31 mg, 65%). The sensitive product was isolated in analytically pure form and could be analyzed by  $^1\text{H}$  NMR. However, in our hands, the compound decomposed in solution before satisfactory  $^{13}\text{C}$  NMR could be obtained. The compound was fully characterized after acylation to afford 4-bromoacetophenone.

$^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ )  $\delta$  (ppm): 7.47 (s, 4H), 7.22 (t,  $J = 7.6$  Hz, 2H), 7.07 (d,  $J = 7.6$  Hz, 4H), 6.27 (s, 2H), 2.59 (sep.,  $J = 6.8$  Hz, 4H), 1.52 (d,  $J = 6.8$  Hz, 12H), 1.09 (d,  $J = 6.8$  Hz, 12H).

#### 4-bromoacetophenone, 4.14

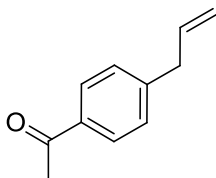


In a glovebox, (IPr)CuF (141 mg, 0.301 mmol) and THF (3 mL) were added to a 25 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with rubber septum and removed from the glovebox. 4-Bromo(triethoxysilyl)benzene (80 mg, 0.251 mmol) added via syringe to afford the organocopper complex, formed in 100% yield by NMR analysis (selected resonances  $^1\text{H}$  NMR (400 MHz,  $\text{THF}-d_8$ ):  $\delta$  (ppm) 7.49 (t,  $J = 7.7$  Hz, 2H), 7.35 (d,  $J = 7.7$  Hz, 4H), 7.31 (s, 2H), 6.85 (m, 2H), 6.80 (m, 2H), 2.71 (sep.,  $J = 6.9$  Hz, 4H), 1.34 (d,  $J = 6.9$  Hz, 12H), 1.25 (d,  $J = 6.9$  Hz, 12H)).

The solution of the organocopper complex was treated with acyl chloride (47 mg, 0.301 mmol) at rt. The reaction was then stirred for 12 h. The solution was filtered through celite. The solution was diluted with ether, washed with water, dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The resulting colorless oil was purified by bulb-to-bulb distillation (chamber at 120 °C, 0.3 Torr) to give 37 mg (74% yield) of 4-bromoacetophenone. The spectral data is consistent with published spectral data.<sup>49</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (d,  $J$  = 8.3 Hz, 2H), 7.61 (d,  $J$  = 8.3 Hz, 2H), 2.59 (s, 3H). IR (film) 3336, 3087, 3060, 2962, 2920, 1677, 1639, 1614, 1588, 1482, 1418, 1396, 1363, 824  $\text{cm}^{-1}$ .

#### 4'-propenyl-acetophenone, 4.15



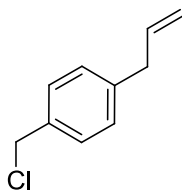
In a glovebox, (IPr)CuF (220 mg, 0.469 mmol) and THF (4.5 mL) were added to a 25 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with rubber septum and removed from the glovebox. 4-(triethoxysilyl)acetophenone (110 mg, 0.391 mmol) was added via

syringe to afford the organocopper complex, formed in quantitative yield by NMR analysis (selected resonances  $^1\text{H}$  NMR (400 MHz, THF-*d*8):  $\delta$  7.47 (t,  $J$  = 7.8 Hz, 2H), 7.35 (d,  $J$  = 7.8 Hz, 4H), 7.31 (s, 2H), 7.27 (d,  $J$  = 8.0 Hz, 2H), 7.07 (d,  $J$  = 8.0 Hz, 2H), 2.72 (sep.,  $J$  = 6.9 Hz, 4H), 2.27 (s, 3H), 1.35 (d,  $J$  = 6.9 Hz, 12H), 1.26 (d,  $J$  = 6.9 Hz, 12H)).

The solution of the organocopper complex was treated with allyl bromide (57 mg, 0.469 mmol) at rt. The reaction was then stirred for 12 h. The solution was filtered through celite, diluted with ether, washed with water, dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The resulting colorless oil was purified by bulb-to-bulb distillation (chamber at 120  $^\circ\text{C}$ , 0.3 Torr) to give 44 mg (88% yield) of 4'-propenyl- acetophenone. The  $^1\text{H}$  data is identical to published spectral data.<sup>50</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 7.89 (d,  $J$  = 8.2 Hz, 2H), 7.28 (d,  $J$  = 8.2 Hz, 2H), 5.99-5.90 (1H, m), 5.12-5.08 (m, 2H), 3.44 (d,  $J$  = 6.65 Hz, 2H), 2.58 (s, 3H). IR (film) 3046, 3005, 2910, 1638, 1597  $\text{cm}^{-1}$ .

**1-(chloromethyl)-4-(2-propenyl)-benzene, 4.16**

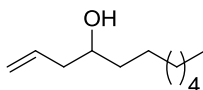


Note: The organocopper complex does not form in 100% yield by NMR analysis due to the extreme electrophilicity of the benzyl chloride substituent. In the absence of electrophile, it can be observed in ca. 20% yield at early stages of the transmetalation before transmetalation

become competitive with decomposition. In the presence of allyl bromide, trapping is rapid and the organocopper species is not observed] In a glovebox, (IPr)CuF (114 mg, 0.243 mmol) and THF (2.5 mL) were added to a 25 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with rubber septum and removed from the glovebox. Allyl bromide (29 mg, 0.243 mmol) and [4- (Chloromethyl)phenyl]trimethoxysilane (50 mg, 0.203 mmol) were added via syringe. The reaction was then stirred for 23 days. The solution was filtered through celite and the solvent removed under reduced pressure. The resulting colorless oil was purified by bulb-to-bulb distillation (chamber at 100 °C, 0.3 Torr) to give 49 mg (82% yield) of 1-(chloromethyl)-4-(2-propenyl)-benzene. Data is consistent with published spectral data.<sup>51</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  (ppm) 7.33 (d,  $J$  = 8.0 Hz, 2H), 7.20 (d,  $J$  = 8.0 Hz, 2H), 5.96 (m, 1H), 5.14-5.06 (m, 2H), 4.59 (s, 2H), 3.40 (d,  $J$  = 6.8 Hz, 2H).

#### 1-undecen-4-ol, 4.17

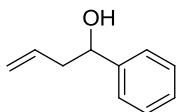


In a glovebox, (IPr)CuF (48 mg, 0.102 mmol) and THF (4 mL) were added to a 25 mL round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with a rubber septum and removed from the glovebox. Allyltrimethoxysilane (399 mg, 2.46 mmol) and octanal (263 mg, 2.05 mmol) were added via syringe. The reaction mixture was then stirred for 2 d. The

reaction was quenched with aq HCl (1 mL, 2M soln). The organic layer was diluted with ether (15 mL), washed with water (15 mL), dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The product was then filtered through a 5 cm silica gel plug washing with 20:1 hexanes/ether to afford the title compound (298 mg, 85%). The  $^1\text{H}$  data is consistent with the published spectral data.<sup>52</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  (ppm) 5.85 (m, 1H), 5.18-5.02 (m, 2H), 3.64 (m, 1H), 2.29-2.25 (m, 2H), 2.20-2.11 (m, 2H), 1.71 (bs, 1H), 1.49-1.28 (m, 10H), 0.89 (t,  $J = 7.0$  Hz, 3H).

**General procedure for catalyzed allylation: Synthesis of 1-phenyl-but-3-en-1-ol, 4.18**

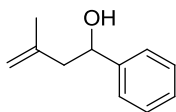


In a glove box, a 20-mL scintillation vial equipped with a Teflon-coated stir bar and a rubber septum was charged with  $(\text{IPr})\text{CuF}$  (22.4 mg, 0.047 mmol) and anhydrous THF (4.0 mL). The vial was then taken out of the glove box and sealed with electrical tape. Octyltrifluorosilane (19.0 mg, 0.096 mmol) and allyltrimethoxysilane (229.1 mg, 1.41 mmol) were added to the solution by syringe and the mixture was stirred for 5 min. Benzaldehyde (100 mg, 0.942 mmol), previously redistilled to remove traces of benzoic acid, was added to the solution and the mixture was stirred for 48 h. The reaction was then quenched with aq HCl (0.1 mL, 2 N soln) and stirred for 1 h. Ether (15 mL) was added, and the mixture was washed with water ( $2 \times 50$  mL) and brine (50 mL). The organic layer was dried over  $\text{MgSO}_4$  and concentrated under vacuum. Kugelrohr distillation (chamber at  $100^\circ\text{C}$ , 15 torr) of the

residue afforded the final product (113 mg, 81%) as a colorless oil. Spectral data is consistent with that previously reported.<sup>53</sup>

GC/MS,  $m/z$ :  $t_R$  = 7.89 min;  $[M]^+$  calcd, 148.2; found, 148.1; (> 95%).

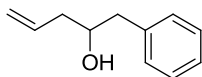
#### 1-phenyl-3-methyl-3-buten-1-ol, 4.19



The procedure described for **4.18** was followed using (IPr)CuF (22.4 mg, 0.047 mmol), cetyltrifluorosilane (19.0 mg, 0.096 mmol), (2-methyl-2-propenyl)triethoxysilane (310.6 mg, 1.42 mmol) and benzaldehyde (100.0 mg, 0.942 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 115.5 mg (75%) of a colorless oil. Data was comparable to that available in the literature.<sup>54</sup>

GC/MS,  $m/z$ :  $t_R$  = 8.61 min;  $[M]^+$  calcd, 162.2; found, 162.1; (> 95%).

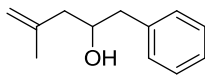
#### 1-phenyl-4-penten-2-ol, 4.20



The procedure described for **4.18** was followed using (IPr)CuF (19.6 mg, 0.042 mmol), octyltrifluorosilane (16.4 mg, 0.083 mmol), allyltrimethoxysilane (202.2 mg, 1.25 mmol) and phenylacetaldehyde (100.0 mg, 0.832 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 98.6 mg (73%) of a colorless oil. Data was comparable to that available in the literature.<sup>55</sup>

GC/MS, *m/z*: tR = 8.66 min; [M ]+ calcd, 162.2; found, 162.1; (> 95%).

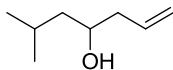
#### 4-methyl-1-phenyl-4-penten-2-ol, 4.21



The procedure described for **4.18** was followed using (IPr)CuF (19.6 mg, 0.042 mmol), octyltrifluorosilane (16.4 mg, 0.083 mmol), (2-methyl-2-propenyl)triethoxysilane (271.6 mg, 1.25 mmol) and phenylacetaldehyde (100.0 mg, 0.832 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 105.0 mg (71.6%) of a colorless oil. Data was comparable to that available in the literature.<sup>56</sup>

GC/MS, *m/z*: tR = 9.31 min; [M]+ calcd, 176.3; found, 176.1; (> 95%).

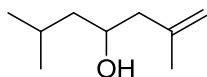
#### 2-methyl-5-hexen-3-ol, 4.22



The procedure described for **4.18** was followed using (IPr)CuF (32.0 mg, 0.068 mmol), octyltrifluorosilane (28.0 mg, 0.14 mmol), allyltrimethoxysilane (337.0 mg, 2.08 mmol) and isobutyraldehyde (100.0 mg, 1.34 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 89.2 mg (56%) of a colorless oil. Data was comparable to that available in the literature.<sup>57</sup>

GC/MS, *m/z*: tR = 3.79 min; [M – C<sub>3</sub>H<sub>7</sub>]<sup>+</sup> calcd, 71.1; found, 71.1; (> 95%).

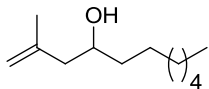
**2,5-dimethyl-5-hexen-3-ol, 4.23**



The procedure described for **4.18** was followed using (IPr)CuF (32.0 mg, 0.068 mmol), octyltrifluorosilane (28.0 mg, 0.14 mmol), (2-methyl-2-propenyl)triethoxysilane (453.8 mg, 2.08 mmol) and isobutyraldehyde (100.0 mg, 1.34 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 115.6 mg (65%) of a colorless oil. Data was comparable to that available in the literature.<sup>58</sup>

GC/MS, *m/z*: tR = 3.66 min; [M – C<sub>3</sub>H<sub>7</sub>]<sup>+</sup> calcd, 85.1; found, 85.2; (> 95%).

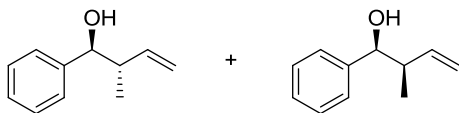


**2-methyl-1-undecen-4-ol, 4.25**

The procedure described for **4.18** was followed using (IPr)CuF (18.4 mg, 0.039 mmol), octyltrifluorosilane (15.4 mg, 0.078 mmol), (2-methyl-2-propenyl)triethoxysilane (254.8 mg, 1.17 mmol) and octanal (100.0 mg, 0.779 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr) and column chromatography (SiO<sub>2</sub>, 20:1, hexane/EtOAc), affording 100.0 mg (72%) of a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  0.88 (t, *J* = 6.9 Hz, 3 H), 1.2-1.5 (m, 12 H), 1.75 (s, 3 H), 2.09 (dd, *J* = 13.5, 9.5 Hz, 1 H), 2.22 (dd, *J* = 13.5, 3.5 Hz, 1 H), 3.70 (m, 1H), 4.80 (m, 1 H), 4.89 (m, 1 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  14.3, 22.6, 22.9, 25.9, 29.5, 29.9, 32.0, 37.3, 46.4, 68.9, 113.6, 143.1. IR (neat): 723, 889, 1081, 1126, 1275, 1457, 1647, 2856, 2956, 2928, 3075, 3370 cm<sup>-1</sup>. GC/MS, *m/z* (rel. int. %) calculated for [M – C<sub>4</sub>H<sub>9</sub>]<sup>+</sup>, 127.1; found, 127.2 (48), 111.2 (12), 83.2 (10), 69.2 (80), 56.2 (100); tR = 8.32 min; (>95%).

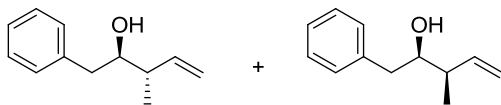
**2-methyl-1-phenyl-3-buten-1-ol, 4.26**



The procedure described for **4.18** was followed using (IPr)CuF (22.4 mg, 0.047 mmol), octyltrifluorosilane (19.0 mg, 0.096 mmol), crotyltrimethoxysilane (250.0 mg, 1.42 mmol) and benzaldehyde (100.0 mg, 0.942 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 120.9 mg (78%) of a colorless oil. The product was identified as a 1:2 mixture of syn and anti diastereomers by NMR.<sup>59</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.89 (d,  $J$  = 6.8 Hz, 2.0 H), 1.03 (d,  $J$  = 6.8 Hz, 1H), 2.20 (s, 1 H), 2.50 (m, 0.67 H), 2.60 (m, 0.33 H), 4.38 (d,  $J$  = 7.2 Hz, 0.67 H), 4.65 (d,  $J$  = 7.2 Hz, 0.33 H), 5.08 (m, 0.67 H), 5.22 (m, 1.33 H), 5.72-5.90 (m, 1 H), 7.21-7.40 (m, 5 H). GC/MS,  $m/z$ : tR = 8.38 min; [M]<sup>+</sup> calcd, 162.2; found, 162.2; (> 95%).

### 3-methyl-1-phenyl-4-penten-2-ol, **4.27**



The procedure described for **4.18** was followed using (IPr)CuF (19.6 mg, 0.042 mmol), octyltrifluorosilane (16.4 mg, 0.083 mmol), crotyltrimethoxysilane (220.0 mg, 1.25 mmol) and phenylacetaldehyde (100.0 mg, 0.832 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 96.7 mg (66%) of a 2.5:1 mixture of the syn and anti

diastereomers. Data was comparable to that available in the literature.<sup>56</sup> The diastereomers are indistinguishable by  $^1\text{H}$  NMR and their ratio was obtained from  $^{13}\text{C}$  NMR.

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.77, 16.6, 40.99, 41.06, 43.25, 43.52, 75.89, 76.0, 115.55, 116.4, 126.56, 126.6, 128.69, 128.75, 129.54, 129.58, 139.12, 139.17, 140.13, 141.13. From the  $^{13}\text{C}$  NMR the ratio between the syn and the anti isomers was calculated to be 2.5:1. GC/MS,  $m/z$ :  $t_R$  = 9.34 min;  $[\text{M}]^+$  calcd, 176.3; found, 176.1; (> 95%).

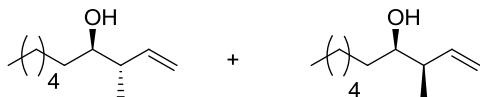
### 2,4-dimethyl-5-hexen-3-ol, 4.28



The procedure described for **4.18** was followed using (IPr)CuF (32.0 mg, 0.068 mmol), octyltrifluorosilane (28.0 mg, 0.14 mmol), crotyltrimethoxysilane (366.5 mg, 2.08 mmol) and isobutyraldehyde (100.0 mg, 1.34 mmol). The product was purified via Kugelrohr distillation (chamber at 100 °C, 15 torr), affording 108.4 mg (61%) of a 4:1 mixture of syn and anti diastereomers. Data was comparable to that available in the literature.<sup>60</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.93 (d,  $J$  = 7.2 Hz, 3 H), 0.97 (d,  $J$  = 6.8 Hz, 3 H), 1.03 (d,  $J$  = 6.8 Hz, 3 H), 1.75 (m, 1 H), 2.25-2.45 (m, 1 H), 3.10 (dd,  $J$  = 5.6, 5.6 Hz, 0.80 H), 3.17 (dd,  $J$  = 6.6 Hz, 0.20 H), 5.0-5.15 (m, 2 H), 5.7-5.9 (m, 1 H). GC/MS,  $m/z$ :  $t_R$  = 3.40 min (anti isomer);  $[\text{M} - \text{C}_3\text{H}_7]^+$  calcd, 85.1; found, 85.1;  $t_R$  = 3.58 min (syn isomer);  $[\text{M} - \text{C}_3\text{H}_7]^+$  calcd, 85.1; found, 85.1; (> 95% for sum of two isomers).

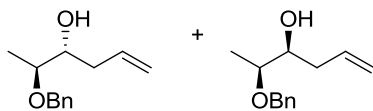
### 3-methyl-1-undecen-4-ol, 4.29



The procedure described for **4.18** was followed using (IPr)CuF (18.4 mg, 0.039 mol), octyltrifluorosilane (15.4 mg, 0.078 mmol), crotyltrimethoxysilane (207.5 mg, 1.17 mmol) and octanal (100.0 mg, 0.779 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 114.4 mg (79.3%) of a colorless oil as a 1:3 mixture of syn:anti diastereomers. Data was comparable to that available in the literature.<sup>61</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  0.88 (t, *J* = 7.2 Hz, 3 H), 1.03 (d, *J* = 7.2 Hz, 2.25 H), 1.04 (d, *J* = 6.8 Hz, 0.75 H), 1.2-1.5 (m, 12 H), 2.10-2.35 (m, 1H), 3.35 (m, 0.75 H), 3.5 (m, 0.25 H), 5.0-5.2 (m, 2 H), 5.7-5.9 (m, 1 H). GC/MS, *m/z*: tR = 8.08 min (anti isomer); [M – C<sub>4</sub>H<sub>9</sub>]<sup>+</sup> calcd, 127.1; found, 127.2; tR = 8.16 min (syn isomer); [M – C<sub>4</sub>H<sub>9</sub>]<sup>+</sup> calcd, 127.1; found, 127.2; (> 95% for sum of two isomers).

**(S,S)-2-(benzyloxy)hex-5-en-3-ol and (S,R)-2-(benzyloxy)hex-5-en-3-ol, 4.30 and 4.31**



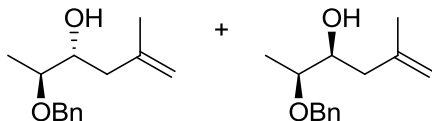
The procedure described for **4.18** was followed using (IPr)CuF (14.4 mg, 0.031 mmol), ctyltrifluorosilane (12.0 mg, 0.060 mmol), allyltrimethoxysilane (148.3 mg, 0.914 mmol) and (S)-2-benzyloxypropanal (100.0 mg, 0.609 mmol). The product was purified via Kugelrohr distillation (chamber at 100 C, 15 torr), affording 107.5 mg (86%) of a colorless oil. The ratio

between the syn and the anti diastereomers, determined by  $^1\text{H}$  NMR, was 1:1.5. Data was comparable to that available in the literature.<sup>62</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.20 (d,  $J = 6.4$  Hz, 2 H), 1.21 (d,  $J = 6$  Hz, 1.2 H), 2.15-2.40 (m, 1.8 H), 3.45 (qd,  $J = 6$  Hz, 0.40 H), 3.51 (m, 1 H), 3.78 (m, 0.60 H), 4.47 (dd,  $J = 25.2, 11.2$  Hz, 1 H), 4.64 (dd,  $J = 18, 11.6$  Hz, 1 H), 5.0-5.20 (m, 2 H), 5.75-6.0 (m, 1 H), 7.20-7.40 (m, 5 H).

GC/MS,  $m/z$ : tR = 10.56 min (syn isomer);  $[\text{M} - \text{C}_3\text{H}_5]^+$  calcd, 165.2; found, 165.1; tR = 10.60 min (anti isomer);  $[\text{M} - \text{C}_3\text{H}_5]^+$  calcd, 165.2; found, 165.1; (>95% for sum of two isomers).

**(S,S)-2-methyl-5-(phenylmethoxy)hex-1-en-4-ol and (S,R)-2-methyl-5-(phenylmethoxy)hex-1-en-4-ol, 4.32 and 4.33**

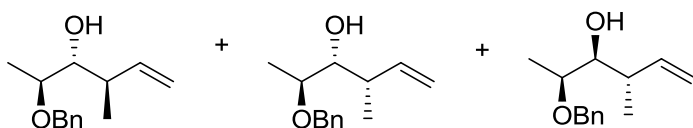


The procedure described for **4.18** was followed using (IPr)CuF (14.4 mg, 0.031 mmol), octyltrifluorosilane (12.0 mg, 0.060 mmol), (2-methyl-2-propenyl)triethoxysilane (199.0 mg, 0.914 mmol) and (S)-2-benzyloxypropanal (100.0 mg, 0.609 mmol). The product was purified via Kugelrohr distillation (chamber at 100 °C, 15 torr) and column chromatography ( $\text{SiO}_2$ , 4:1, hexane/EtOAc), affording 100.7 mg (75%) of a colorless oil as a 1:1.9 syn/anti mixture. Data was comparable to that available in the literature.<sup>63</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.21 (d,  $J = 6.4$  Hz, 1.97 H), 1.22 (d,  $J = 6$  Hz, 1.03 H), 1.75 (s, 3 H), 2.1-2.3 (m, 1 H), 3.46 (qd,  $J = 6.4$  Hz, 0.34 H), 3.51 (m, 0.66 H), 3.65 (m, 0.34 H), 3.87 (m,

0.66 H), 4.49 (dd,  $J = 25.2, 11.2$  Hz, 1 H), 4.65 (dd,  $J = 18, 11.6$  Hz, 1 H), 4.78-4.9 (m, 2 H), 7.22-7.40 (m, 5 H). GC/MS,  $m/z$ :  $t_R = 11.15$  min (anti isomer);  $[M - C_4H_7]^+$  calcd, 165.2; found, 165.1;  $t_R = 11.18$  min (syn isomer);  $[M - C_4H_7]^+$  calcd, 165.2; found, 165.1; (> 95% for sum of two isomers).

**(2S,3R,4R)-2-(benzyloxy)-4-methyl-5-hexen-3-ol, (2S,3R,4S)-2-(benzyloxy)-4-methyl-5-hexen-3-ol and (2S,3S,4S)-2-(benzyloxy)-4-methyl-5-hexen-3-ol, 4.34, 4.35 and 4.36**



The procedure described for **4.18** was followed using (IPr)CuF (14.4 mg, 0.031 mmol), octyltrifluorosilane (12.0 mg, 0.060 mmol), crotyltrimethoxysilane (160.0 mg, 0.914 mmol) and (S)-2-benzyloxypropanal (100.0 mg, 0.609 mmol). The product was purified via Kugelrohr distillation (chamber at 100 °C, 15 torr), affording 115.2 mg (85%) of a colorless oil. The ratio and the identity of the diastereomers was determined by  $^{13}C$  NMR and GC-MS, and was calculated to be 1:3.4:1.14, (2S,3S,4S):(2S,3R,4R):(2S,3R,4S). The amount of diastereomer (2S,3R,4R) was less than 5% of the material. Data was comparable to that available in the literature.<sup>64</sup>

$^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  0.99 (d,  $J = 7.2$  Hz, 1.84 H), 1.08 (d,  $J = 5.6$  Hz, 0.63 H), 1.10 (d,  $J = 5.6$  Hz, 0.53 H), 1.90 (d,  $J = 6.4$  Hz, 0.53 H), 1.92 (d,  $J = 7.2$  Hz, 0.63 H), 1.22 (d,  $J = 6$  Hz, 1.84 H), 2.25-2.40 (m, 0.37 H), 2.40-2.50 (m, 0.63 H), 3.55 (m, 2 H), 4.48 (dd,  $J = 25.2, 11.2$  Hz,

1 H), 4.60 (dd,  $J = 18, 11.6$  Hz, 1 H), 4.95-5.08 (m, 0.73 H), 5.08-5.19 (m, 1.92 H), 5.66 (ddd,  $J = 18.8, 10.8, 8$  Hz, 0.26 H), 5.86 (ddd,  $J = 18, 10, 8$  Hz, 1 H), 7.21-7.41 (m, 7.22 H). GC/MS,  $m/z$ :  
tR = 10.92 min (2S,3R,4S isomer);  $[M - C_4H_7]^+$  calcd, 165.2; found, 165.1; tR = 10.97 min  
(2S,3S,4S isomer);  $[M - C_4H_7]^+$  calcd, 165.2; found, 165.1; tR = 11.18 min (2S,3R,4R isomer);  
 $[M - C_4H_7]^+$  calcd, 165.2; found, 165.1; (> 95% for sum of three isomers).

#### 4.10 References

- (1) Yang, X. Y.; Rotter, T.; Piazza, C.; Knochel, P. *Org. Lett.* **2003**, *5*, 1229.
- (2) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681.
- (3) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W. W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132.
- (4) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 8656.
- (5) Piers, E.; McEachern, E. J.; Burns, P. A. *J. Org. Chem.* **1995**, *60*, 2322.
- (6) Sun, H. R.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050.
- (7) Gulliver, D. J.; Levason, W.; Webster, M. *Inorganica Chimica Acta-Articles* **1981**, *52*, 153.
- (8) Franz, A. K.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 949.
- (9) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811.
- (10) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450.
- (11) Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 985.
- (12) Lermontov, S. A.; Rakov, I. M.; Zefirov, N. S.; Stang, P. J. *Tetrahedron Lett.* **1996**, *37*, 4051.



- (13) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138.
- (14) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536.
- (15) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
- (16) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910.
- (17) Pilcher, A. S.; Ammon, H. L.; Deshong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.
- (18) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901.
- (19) Healy, P. C.; Kildea, J. D.; Skelton, B. W.; Waters, A. F.; White, A. H. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1991**, *47*, 1721.
- (20) Chaudhuri, M. K.; Dhar, S. S.; Vijayashree, N. *Transition Met. Chem.* **2000**, *25*, 559.
- (21) Mori, A.; Fujita, A.; Nishihara, Y.; Hiyama, T. *Chem. Commun.* **1997**, 2159.
- (22) Straub, B. F.; Rominger, F.; Hofmann, P. *Inorg. Chem.* **2000**, *39*, 2113.
- (23) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036.
- (24) Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 1191.
- (25) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369.
- (26) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417.
- (27) Blue, E. D.; Gunnoe, T. B.; Petersen, J. L.; Boyle, P. D. *J. Organomet. Chem.* **2006**, *691*, 5988.
- (28) Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Pierpont, A. W.; Petersen, J. L.; Boyle, P. D. *Inorg. Chem.* **2006**, *45*, 9032.

- (29) Munro-Leighton, C.; Delp, S. A.; Blue, E. D.; Gunnoe, T. B. *Organometallics* **2007**, 26, 1483.
- (30) Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, 23, 1157.
- (31) Diez-Gonzalez, S.; Nolan, S. P. *Synlett* **2007**, 2158.
- (32) Laitar, D. S., Ph.D. Thesis. Massachusetts Institute of Technology, Cambridge, MA, 2006.
- (33) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, 112, 4404.
- (34) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Org. Chem.* **1989**, 54, 4977.
- (35) Szabo, K. J. *Chem. Eur. J.* **2000**, 6, 4413.
- (36) Hope, H.; Olmstead, M. M.; Power, P. P.; Sandell, J.; Xu, X. *J. Am. Chem. Soc.* **1985**, 107, 4337.
- (37) Lorenzen, N. P.; Weiss, E. *Angew. Chem. Int. Ed.* **1990**, 29, 300.
- (38) Solin, N.; Kjellgren, J.; Szabo, K. J. *J. Am. Chem. Soc.* **2004**, 126, 7026.
- (39) Denmark, S. E.; Fu, J. P. *Chem. Rev.* **2003**, 103, 2763.
- (40) Lee, K.-S.; Hoveyda, A. H. *J. Org. Chem.* **2009**, 74, 4455.
- (41) Anh, N. T.; Eisenstein, O. *Nouveau Journal De Chimie-New Journal of Chemistry* **1977**, 1, 61.
- (42) Ohishi, T.; Nishiura, M.; Hou, Z. M. *Angew. Chem. Int. Ed.* **2008**, 47, 5792.
- (43) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, 66, 7729.
- (44) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, 606, 49.
- (45) Manoso, A. S.; Ahn, C.; Soheili, A.; Handy, C. J.; Correia, R.; Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, 69, 8305.
- (46) Manoso, A. S.; DeShong, P. *J. Org. Chem.* **2001**, 66, 7449.

- (47) Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* **2002**, *4*, 1843.
- (48) There are small discrepancies in our  $^1\text{H}$  NMR spectra from that reported by Gunnoe (38 H are reported; the structure requires 41 H). The  $^{13}\text{C}$  NMR data are consistent and we assume the discrepancies are due to clerical error.
- (49) Qian, W. X.; Jin, E. L.; Bao, W. L.; Zhang, Y. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 952.
- (50) Lee, P. H.; Sung, S. Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201.
- (51) Parr, W.; Grohmann, K. *Angew. Chem. Int. Ed.* **1972**, *11*, 314.
- (52) Yao, Q. W.; Sheets, M. *J. Org. Chem.* **2006**, *71*, 5384.
- (53) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.
- (54) Rieke, R. D.; Klein, W. R.; Wu, T. C. *J. Org. Chem.* **1993**, *58*, 2492.
- (55) Barentsen, H. M.; Sieval, A. B.; Cornelisse, J. *Tetrahedron* **1995**, *51*, 7495.
- (56) McCluskey, A.; Muderawan, I. W.; Muntari; Young, D. J. *J. Org. Chem.* **2001**, *66*, 7811.
- (57) Wada, M.; Ohki, H.; Akiba, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738.
- (58) Miura, K.; Wang, D.; Hosomi, A. *J. Am. Chem. Soc.* **2005**, *127*, 9366.
- (59) Tokuda, M.; Satoh, S.; Suginome, H. *J. Org. Chem.* **1989**, *54*, 5608.
- (60) Helm, M. D.; Mayer, P.; Knochel, P. *Chem. Commun.* **2008**, 1916.
- (61) Dinh, T. Q.; Du, X. H.; Smith, C. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 6773.
- (62) Stojanovic, A.; Renaud, P.; Schenk, K. *Helv. Chim. Acta* **1998**, *81*, 268.
- (63) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214.
- (64) Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 6129.



# Chapter 5

## Copper (I) Fluoride Complexes for Catalytic Organosilane Reactivity

Parts of this chapter have been adapted from:

Herron, J. R.; Russo, V.; Valente, E. J.; Ball, Z. T. "Catalytic Organocopper Chemistry from Organosiloxane Reagents." *Chem. Eur. J.* **2009**, 15, 8713

### 5.1 Introduction

The search for increasingly selective and environmentally benign methods continues to be of importance to synthetic methodology. Organosilane reagents are important in this regard because they are typically stable to a wide range of functional groups and reaction conditions, allowing selective chemical transformations in multifunctional molecules (Chapter 2).<sup>1</sup> In addition, organosilanes are generally inexpensive and produce innocuous and easily removed polysiloxane byproducts. However, the classical use of organosilanes as carbon nucleophiles for C-C bond formation is generally limited to intramolecular processes or reactions with extremely reactive electrophiles. We here report the intermolecular coupling of organosilanes with vinyl epoxides and later intramolecular cyclization of organosilanes to  $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of a copper catalyst.

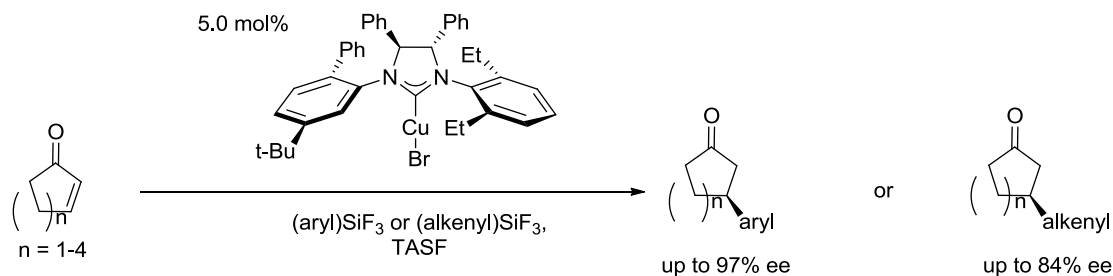
Functional-group-tolerant synthetic methods of organosilanes can be developed through activation and transmetalation with a transition-metal catalyst to produce new, more reactive

organometallic intermediates. This approach has been successfully applied to palladium-catalyzed cross-coupling chemistry (Chapter 2), typically utilizing fluoride activation of the silane.<sup>2-9</sup> However, the kinetic stability and strong C-Si bonds of organosilanes have limited the use of organosilane precursors for catalytic generation of other organometallic intermediates.<sup>10</sup> A few reports of rhodium-catalyzed reactivity have appeared,<sup>11-20</sup> but rhodium and palladium processes typically occur in the presence of water, allowing the intermediacy of silanolates which are thought to facilitate transmetalation.<sup>21</sup> Aqueous conditions are possible since these organometallics are relatively stable to proteolytic decomposition. Extension of these ideas to other transition metals is challenging because many synthetically important transition-metal organometallics, such as those of copper, are unstable with respect to protonolysis in the presence of water, thus preventing the addition of water to allow access to silanoate intermediates.

Focusing on copper-catalyzed activation of organosilanes, important early work demonstrated the feasibility of this approach with readily transferrable groups such as alkynyl and allylsilanes.<sup>22-24</sup> Beyond these substrate classes, demonstration of organocopper reactivity from organosilanes is generally limited to specially activated substrates.<sup>25-29</sup> Copper-based organosilane C-C bond formation processes include alkenylsilane dimerization with stoichiometric copper<sup>30,31</sup> and catalytic 1,2-addition to aldehydes.<sup>32</sup> In these cases, organocopper intermediates can be inferred on the basis of available evidence, but care must be taken since fluoride can activate organosilanes for C-C bond formation and it can be difficult to distinguish transmetalation pathways from silicate reactivity.<sup>33,34</sup> Copper salts have come into use as additives in palladium cross coupling, and they show beneficial effects with organosilane substrates as well,<sup>35</sup> the role of copper in these palladium-catalyzed reactions is not well understood. Stoichiometric fluoride activators are typically employed in silane activation chemistry, yet few stable, anhydrous fluoride sources are soluble in apolar, aprotic solvents.<sup>36</sup> Studying copper(I) chemistry in the presence of fluoride is further challenging due to disproportionation of CuF in the absence of appropriate stabilizing ligands.<sup>37</sup>

More recently, Hoveyda and coworkers described an enantioselective conjugate addition to cyclic enones employing organo(trifluoro)silanes as nucleophiles in the presence of a fluoride additive<sup>38</sup> (Scheme 1). In the Hoveyda work, excellent yields and enantioselectivities are achieved. There is little benefit in the way copper species bearing significant molecular complexity are generated due to the harsh nature in which organo(trifluoro)silanes are synthesized.

**Scheme 1. Enantioselective copper-catalyzed conjugate addition of organo(trifluoro)silanes to cyclic enones. Figure adapted from reference 38.**

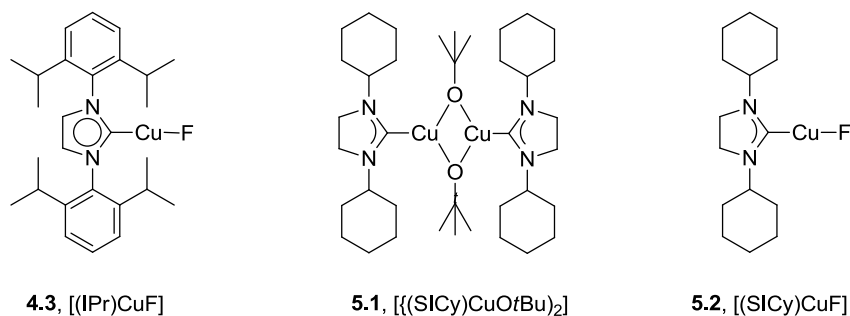


## 5.2 Intermolecular reactivity

To develop silane-based methods for organocopper reactivity, such as addition to electron-deficient olefins, we previously examined the transmetalation of organosilanes with a well-defined copper(I) fluoride complex **4.3**<sup>39</sup> (Chapter 4). In that initial report, we were able to demonstrate clean transmetalation of arylsilanes to afford stable aryl copper compounds and to demonstrate the feasibility of C-C bond-forming reactions of these intermediates. However, the

sluggish reactivity of copper complexes with the IPr ligand (IPr=1,3-bis(2',6'-diisopropylphenyl)imidazol-2-ylidene) in transmetalation and C-C bond-forming reactions prevented its extension into a general catalytic process.<sup>40</sup> Treatment of complex **4.3** with phenyltrimethoxysilane in THF results in the quantitative formation of [(IPr)CuPh], but the process is rather slow, requiring about 2 h to reach complete conversion. More troublesome, the [(IPr)CuPh] complex exhibits limited reactivity: [(IPr)CuPh] does not react at all with butadiene monoepoxide at ambient temperature, and eventually decomposition is observed at elevated temperatures.

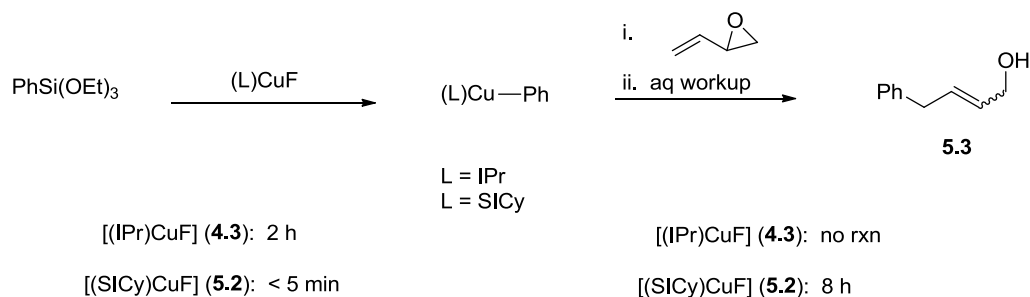
**Figure 1. NHC copper complexes**



To improve reactivity, we examined other ligands, settling on the saturated ligand dicyclohexylimidazolin-2-ylidene (SICy).<sup>41</sup> The choice was based on the reasoning that the decreased steric demand and increased electron-donating ability might improve reactivity. Stoichiometric reactivity studies confirm this straightforward hypothesis. The complex [(SICy)CuF] is readily available upon treatment of the dimeric tert-butoxide complex with Et<sub>3</sub>N·3HF.<sup>42</sup>

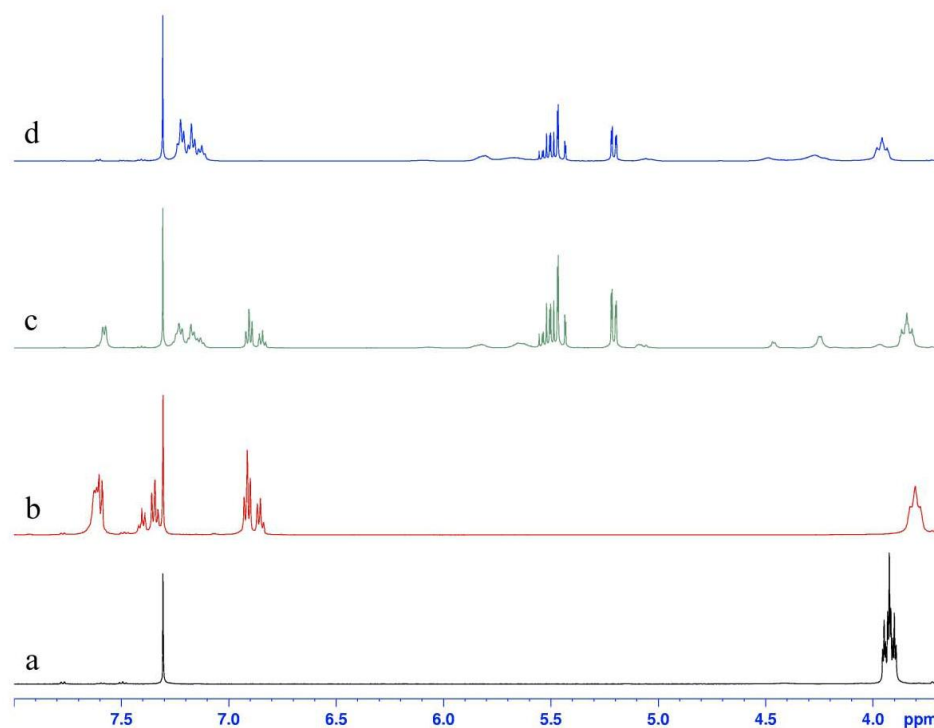


**Scheme 2. Reactivity of N-heterocyclic carbene-copper complexes in transmetalation and conjugate addition reactions.**



In a stoichiometric study analyzed by  $^1\text{H}$  NMR spectroscopy, transmetalation of trimethoxyphenylsilane with the [(SICy)CuF] complex (**5.2**) proceeds in less than 5 min at ambient temperature, and the organocopper compound reacts cleanly, though slowly, with butadiene monoepoxide, also at ambient temperature (Scheme 2). The stoichiometric reaction of the phenylcopper species with butadiene monoepoxide took 8 h to reach completion (Figure 2), indicating that C-C bond formation may well be turnover-limiting in catalytic reactions.

**Figure 2.**  $^1\text{H}$  NMR spectra of the stoichiometric reaction between (SiCy)CuF, PhSi(OMe) $_3$  and butadiene monoepoxide in THF  $d_8$ . a) (SiCy)CuF in THF  $d_8$  (the singlet at 7.3 ppm is a C $_6\text{H}_6$  reference peak); b) (SiCy)CuF + 1 eq PhSi(OMe) $_3$ , after 5 min; c) (SiCy)CuPh + 1 eq butadiene monoepoxide, after 4 h; d) (SiCy)CuPh + 1 eq butadiene monoepoxide, after 17 h.



Despite concerns about our ability to generate turnover in the absence of a stoichiometric fluoride activator, we were overjoyed to find that complex **5.2** is a competent catalyst for the formation of alcohol **5.3** (Table 1, entry 1), proceeding in good yield at ambient temperature.<sup>43</sup> The reaction appears general for aryl and heteroaryl silanes. Substitution at the ortho position is well tolerated (Table 1, entries 6 and 7), and electron-poor as well as electron-rich arene rings succeed as nucleophiles (Table 1, entries 3 and 4). In addition, the use of organosilane reagents allows significant functional group tolerance to the coupling reaction. Electrophilic carbonyl

groups (Table 1, entry 4) succeed in the present method, as does an aryl chloride (Table 1, entry 8). In addition to trialkoxysilanes, catalytic activation proceeds cleanly with monoalkoxysilanes (Table 1, entries 2, 8, 11). This is a significant synthetic benefit, as monoalkoxysilanes have increased stability towards hydrolysis and are readily purified by silica gel chromatography.

A variety of vinyl epoxide substitution patterns are also tolerated. In acyclic cases, only the 1,4-addition product is observed, but a cyclic epoxide (Table 1, entry 13) gave minor amounts of the 1,2-addition product **5.14b** in addition to the expected product **5.14a**. Both products **5.14a** and **5.14b** are isolated with strictly anti stereochemistry, resulting from clean attack on the face opposite the epoxide leaving group.

In addition to aryl and heteroaryl silanes, activated sp<sup>3</sup>-organosilanes also participate. Benzyl- and 2-furylmethylsilanes (Table 1, entries 10, 11) couple successfully in the catalytic process. Whereas aryl silane reagents afford mixtures of olefin isomers, reactions of these sp<sup>3</sup>-organosilanes exhibit

significant bias for the formation of the (*E*)-olefin product. Benzyltriethoxysilane is an example of the increased reactivity of [(SICy)CuF] (**5.2**) relative to [(IPr)CuF] (**4.3**) in transmetalation reactions in addition to C-C bond-forming steps. Treatment of [(IPr)CuF] with benzyltriethoxysilane does not result in any benzyl group transmetalation, yet clean catalytic reactivity is observed with [(SICy)CuF] (Table 1, entry 10).

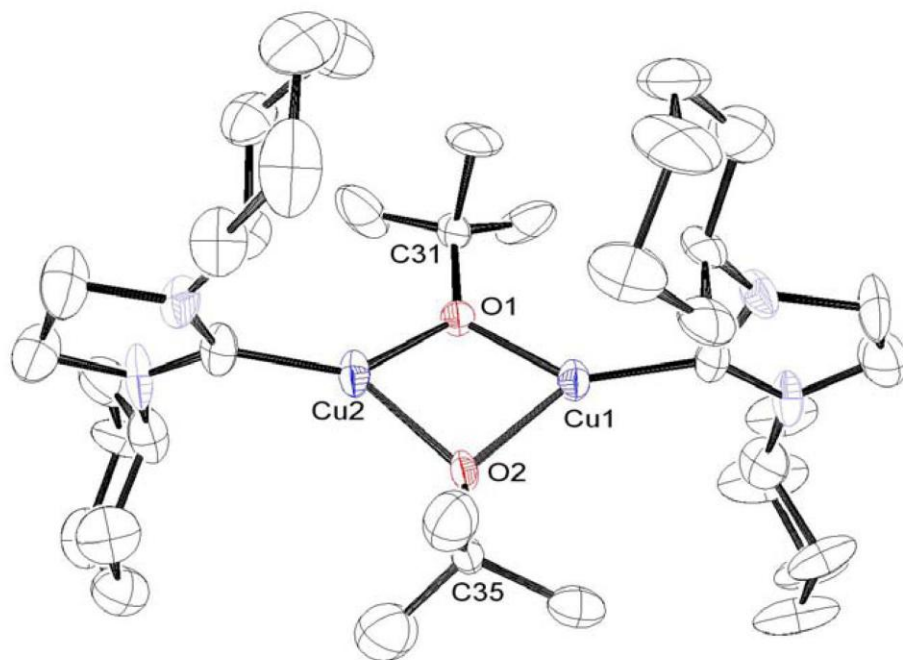
**Table 1. Catalytic coupling of organosiloxanes with vinyloxyepoxides**

entry <sup>a</sup>	silane	epoxide <sup>b</sup>	number	product	yield [%], (E/Z ratio)
1			<b>5.3</b>		72 (2.6:1)
2			<b>5.3</b>		70 (2.0:1)
3			<b>5.4</b>		90 (2.4:1)
4			<b>5.5</b>		65 (1.8:1)
5			<b>5.6</b>		81 (2.0:1)
6			<b>5.7</b>		80 (2.2:1)
7			<b>5.8</b>		82 (1.5:1)
8			<b>5.9</b>		45 (1.5:1)
9			<b>5.10</b>		68 (2.4:1)
10			<b>5.11</b>		70 (3.9:1)
11			<b>5.12</b>		89 (7.8:1)
12			<b>5.13</b>		82 (1.0:1)
13			<b>5.14a</b> <b>5.14b</b>		80 (3:1) <sup>b</sup>

[a] Unless otherwise noted, all reactions began at -78°C, and were immediately allowed to warm to room temperature. The reaction time is 48 h. Products were isolated as a mixture of E/Z isomers, and the isomeric ratio was determined by <sup>1</sup>H NMR spectroscopy or GC-MS analysis. [b] Ratio of 1,4-product to 1,2-product (**5.14a**:**5.14b**). Only products of anti stereochemistry are observed.

The tert-butoxide complex **5.1** is quite unstable, decomposing within hours at ambient temperature. The crystal structure of tert-butoxide **5.1** confirms the presence of a dimer in the solid state consistent with the similar copper tert-butoxide complex,  $[\{(SiPr)-CuOtBu\}_2]$ .<sup>29</sup> By contrast, the fluoride complex  $[(SiCy)CuF]$  is monomeric<sup>42</sup> and is stable indefinitely at room temperature. The dimeric nature of tert-butoxide **5.1** may be taken as evidence for increased accessibility of the copper core and hence of increased reactivity<sup>38</sup> of the SiCy ligand system relative to the  $[(IPr)CuOtBu]$  precursor to **4.3**, which is monomeric in the solid state,<sup>44</sup> indicating that copper fluoride complexes may be more desirable than alkoxide complexes as convenient and stable yet highly reactive NHC-copper(I) complexes. In the case at hand, whether the catalytically active species is a copper fluoride or copper alkoxide is an unanswered question; preliminary NMR evidence indicates that fluoride/ethoxide exchange is faster than transmetalation under relevant reaction conditions.

**Figure 3.** X-Ray Crystallography [1,3-dicyclohexylimidazolin-2-ylidene]copper(I) tert-butoxide, (SiCy)CuOt-Bu, without H-atoms and showing the bridging groups.



### 5.3 Intramolecular reactivity

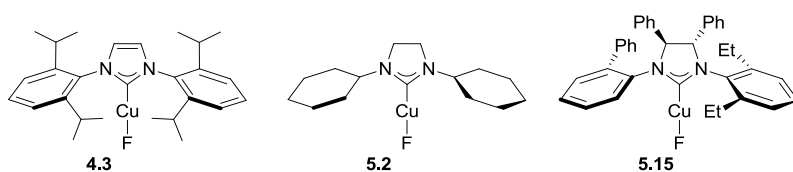
The application of intramolecular organocopper reactivity from precursor organometallics is valuable for target-directed synthesis, but brings with it special challenges. Although it is generally assumed that intramolecular reactivity is more facile than intermolecular coupling, this is not necessarily the case. Performing intramolecular reactions requires that organocopper intermediates can be formed in the presence of sensitive electrophilic functionality, and orientational constraints may be problematic. For example, in our hands, published methods for rhodium-catalyzed intermolecular organosilane conjugate addition fail to catalyze intramolecular reactions.<sup>15-17</sup> Further illustrating the unmet synthetic need, a recent strychnine synthesis achieved a late-stage intramolecular conjugate addition of an organosilane in only 5-10% yield using a Brook

rearrangement approach.<sup>45</sup> To succeed, all steps in the catalytic cycle must accommodate sensitive functionalities such as halides and  $\alpha$ -acidic protons.

To examine intramolecular reactivity of organocopper intermediates derived from organosilane precursors, we synthesized aryl substrate **5.16**. Potential vinyl cyclization precursors can be easily obtained by hydrosilylation of alkynes. Obtaining synthetic precursors via hydrosilylation highlights another advantage of using organosilanes as a stable alternative to heavily relied on organohalides.

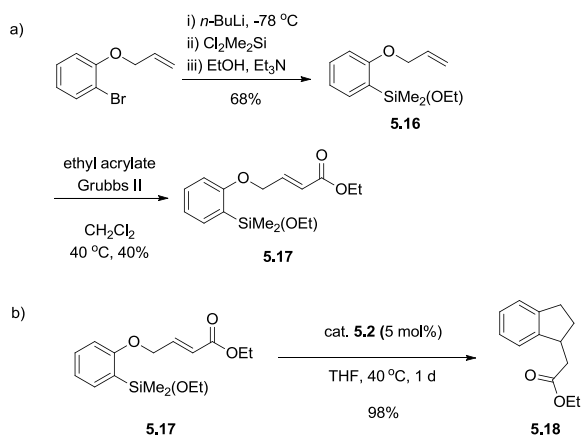
The ability to accomplish conjugate addition reactions is highly dependent on ligand structure (Figure 4). Complex **4.3** facilitates stoichiometric transmetalation with organosilanes,<sup>39</sup> but the transmetalation product does not participate in conjugate addition reactions. Complex **5.2** and **5.15**, however, catalyze both intermolecular and intramolecular conjugate addition reactions depending on the electrophile.

**Figure 4. NHC copper complexes**



The arylsilane substrate was prepared by lithiation of the corresponding arylhalide, followed by trapping with silane (Scheme 3, a).

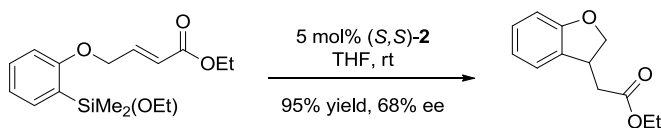
### Scheme 3. Substrate synthesis and cyclization



Submitting arylsilane **5.17** copper complex **5.2** or **5.15** at  $50\text{ }^{\circ}\text{C}$  for 1 d results in nearly quantitative conversion to the desired 5-membered ring (Scheme 3, b). Encouragingly, the ring closure with arylsilane **5.17** and (NHC)CuF **5.15** in THF at  $50\text{ }^{\circ}\text{C}$  affords an enantiomeric excess of 52%. Lowering the temperature to rt increases the ee to 68% (Scheme 4). Unfortunately, lowering the temperature any further prevents the transmetalation from occurring. While the enantioselectivity is modest in the case of the C2-symmetric chiral (NHC) ligand **5.15**, it seems reasonable to presume that other chiral (NHC) ligands could be examined to improve enantioselectivity.<sup>38</sup>



#### Scheme 4. Enantioselectivity



#### 5.4 Concluding remarks

We describe a mild and general catalytic method for accessing organocopper chemistry from organosilane reagents without the need for stoichiometric fluoride additives. Catalytic silane activation could find use in selective chemistry on silicon surfaces in addition to small-molecule synthesis. We anticipate that the concepts described here will allow us to take advantage of the wealth of extant knowledge about asymmetric NHC ligands for catalytic organocopper chemistry<sup>38,46-48</sup> to develop new selective reactions of silanes and to expand this work to new substrate classes.

#### 5.5 Experimental

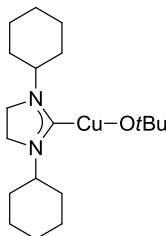
##### General information

All synthetic manipulations were carried out using standard Schlenk techniques under a nitrogen atmosphere or in a nitrogen-atmosphere glovebox. All reactions were carried out in flame- or oven-dried glassware unless otherwise indicated. THF, ether, and benzene were distilled from

sodium benzophenone ketyl under nitrogen. Pentane was sparged with nitrogen and stored in a glovebox. All other solvents were reagent grade. NMR solvents were dried and degassed as follows: C<sub>6</sub>D<sub>6</sub> (Cambridge Isotope Laboratories) over sodium/benzophenone, CD<sub>2</sub>Cl<sub>2</sub> (Cambridge Isotope Laboratories) over P<sub>2</sub>O<sub>5</sub>, and THF-*d*<sub>8</sub> (Cambridge Isotope Laboratories) over sodium/benzophenone. All NMR solvents were degassed with three freeze-pump-thaw cycles and vacuum-transferred prior to use. Flash chromatography was performed with 40-63 μm particle size silica gel. NMR data were acquired with Bruker Avance 400 MHz or Bruker Avance 500 MHz instruments. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded relative to residual standard. <sup>19</sup>F NMR spectra were recorded on a Bruker Avance 500 MHz instrument, with shifts relative to a CFCl<sub>3</sub> standard. GC-MS was conducted on an Agilent 5973N MSD interfaced to an Agilent 6890N GC System equipped with an Rtx-35 MS column. The GC method involved a temperature ramp from 50 to 220 °C over 20 min. IR spectra were recorded using a Nicolet Avatar 320 FT-IR spectrometer. Copper(I) chloride (Strem) and sodium *tert*-butoxide (Acros) were used as received and were stored and weighed in a glovebox. Tetraethyl orthosilicate (Aldrich), triethylamine tris(hydrofluoride) (Acros), 4-(triethoxysilyl)toluene (Gelest), trimethoxyphenylsilane, 4-chloro(triethoxysilyl)benzene (Gelest), 4-(triethoxysilyl)anisole (Gelest), and ethyl 4-(triethoxysilyl)benzoate (Gelest), 3-(triethoxysilyl)-furan (Aldrich), benzyltriethoxysilane (Silar Laboratories), butadiene monoepoxide (Acros), and 2-methyl-2-

vinyl-oxirane (Aldrich) were used as received. 2-(triethoxysilyl)anisole,<sup>49</sup> 2-(triethoxysilyl)toluene,<sup>49</sup> (2-furanylmethyl)methoxydimethyl-silane,<sup>50</sup> 1,3-cyclohexadiene monoepoxide,<sup>51</sup> allyloxy-2-bromobenzene,<sup>52</sup> and chiral imidazolium salt<sup>38</sup> were synthesized according to literature protocols.

**[1,3-dicyclohexylimidazolin-2-ylidene]copper(I) *tert*-butoxide, ((SICy)CuOt-Bu), 5.1**



In the glove box, a suspension of copper(I) chloride (0.915 g, 9.23 mmol) and sodium *tert*butoxide (0.975 g, 10.15 mmol) in tetrahydrofuran (85 mL) was stirred for 1 h. 1,3-dicyclohexylimidazolium chloride (2.50 g, 9.23 mmol) was added to the mixture, and the resulting suspension was stirred for 2 h. The mixture was then filtered through celite and the

solvent removed under vacuum, affording an off-white solid (3.00 g, 97%). Data is consistent

with that previously reported for this compound.  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  3.79 (m, 2 H),

3.48 (s, 4 H), 1.80 (m, 8 H), 1.63 (m, 2 H), 1.49 (m, 4 H), 1.34 (m, 4 H), 1.10 (m, 2 H).

$^{13}\text{C}$

NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  197.8, 60.2, 44.8, 32.5, 25.9, 25.7. In the glove box, a

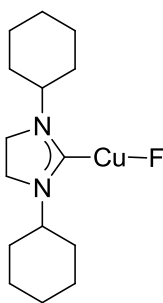
suspension of [1,3-dicyclohexylimidazolin-2-ylidene]copper(I) chloride (2.00 g, 6.00

mmol) and sodium *tert*-butoxide (0.577 g, 6.00 mmol) in anhydrous tetrahydrofuran (40 mL) was stirred for 1.5 h. The mixture was then filtered through celite and concentrated

in vacuo to afford a white solid (2.12 g, 95%). Data is consistent with that previously reported for this compound.<sup>42</sup>

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  4.14 (m, 2 H), 2.66 (s, 4 H), 1.77 (s, 9 H), 1.68 (m, 4 H), 1.57 (m, 4 H), 1.41 (m, 2 H), 1.17 (m, 8 H), 0.85 (m, 1 H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  202.8, 69.4, 59.5, 43.8, 37.8, 32.3, 26.0, 25.9.

**[1,3-dicyclohexylimidazolin-2-ylidene]copper(I) fluoride, ((SICy)CuF), 5.2**

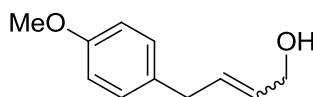


In the glove box, [1,3-dicyclohexylimidazolin-2-ylidene]copper(I) *tert*-butoxide (2.00 g, 5.40 mmol) was placed in a 100-mL round-bottom flask and dissolved in anhydrous benzene (30 mL). The flask was closed with a rubber septum, sealed with electrical tape, and removed from the glove box. Triethylamine tris(hydrofluoride) (0.279 mL, 1.71 mmol) was then added to the solution via syringe, the flask was taken back into the glove box. The mixture was stirred for 30 min. The solvent was removed under vacuum, and the resulting yellow solid was stirred in pentane (10 mL) for 12 h. The suspension was filtered to afford a tan solid (1.45 g, 90%). Data is consistent with that previously reported for this compound.<sup>42</sup>

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  3.90 (m, 2 H), 3.46 (s, 4 H), 1.80 (m, 8 H), 1.65 (m, 2 H), 1.47 (m, 4 H), 1.42 (m, 4 H), 1.09 (m, 2 H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  197.4, 60.2, 44.5, 32.3, 25.9, 25.8.  $^{19}\text{F}$  NMR (470.59 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  -239.7.

### General Procedure for Cu-catalyzed Silane Coupling:

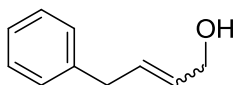
**(*E*)-4-(4-methoxy-phenyl)-but-2-en-1-ol and (*Z*)-4-(4-methoxy-phenyl)-but-2-en-1-ol (5.4).**



In a glovebox, (SICy)CuF (50 mg, 0.158 mmol) and THF (1.0 mL) were added to a 20-mL scintillation vial equipped with a Teflon-coated stirbar. The vial was sealed with a rubber septum and removed from the glovebox. The silane, (4-methoxyphenyl)-triethoxysilane (510 mg, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were added via syringe at -78 °C. The reaction was quenched with HCl (1 mL, 2 N aq soln). The organic layer was diluted with ether (15 mL), washed with water (15 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The crude reaction mixture was taken up in hexane (10 mL) and filtered through celite. The title product was purified by silica gel chromatography (eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol) to afford 252 mg (90% yield) of a colorless oil as a 2.4:1 mixture of olefin isomers. The (*E*) isomer has been previously reported, and the characterization data is consistent with our isolated mixture of olefin isomers.<sup>53</sup>

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.13 (d,  $J = 7.6$  Hz, 2H), 6.85 (d,  $J = 7.6$  Hz, 2H), 5.85 (m, 0.7H), 5.74-5.67 (m, 1.3H), 4.32 (d,  $J = 4.8$  Hz, 0.6H), 4.13 (d,  $J = 6.0$  Hz, 1.4H), 3.81 (s, 3H), 3.39 (d,  $J = 5.6$  Hz, 0.6H), 3.34 (d,  $J = 6.4$  Hz, 1.4H), 1.31 (bs, 1H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  161.0, 135.1, 134.6, 133.0, 132.5, 132.2, 132.0, 117.0, 116.9, 66.5, 61.6, 58.3, 40.8, 35.8. IR (neat): 3365, 2933, 1732, 1610, 1507, 1300, 1244, 1175, 1033  $\text{cm}^{-1}$ . GC-MS: *tR* 11.87 min (>95%), calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_2$ : 178.1, found:  $[\text{M}]^+$  178.1.

**(*E*)-4-phenyl-2-buten-1-ol and (*Z*)-4-phenyl-2-buten-1-ol (5.3).**

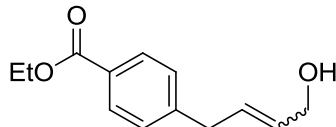


Following the general procedure given for the synthesis of (*E/Z*)-4-(4-methoxy-phenyl)-but-2-en-1-ol,

phenyltrimethoxysilane (373 mg, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (167 mg, 72%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol. The (*E*) isomer has been previously reported, and the characterization data is consistent with our isolated mixture of olefin isomers.<sup>54</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.36-7.32 (m, 2H), 7.27-7.22 (m, 3H), 5.86 (m, 0.7H), 5.78-5.70 (m, 1.3H), 4.32 (d,  $J = 4.4$  Hz, 0.7H), 4.13 (d,  $J = 5.2$  Hz, 1.5H), 3.47 (d,  $J = 5.2$  Hz, 0.5H), 3.32 (d,  $J = 6.8$  Hz, 1.5H), 2.30 (bs, 0.3H), 2.24 (bs, 0.7H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  140.5, 140.3, 131.6, 131.1, 130.6, 129.7, 128.8, 128.7, 128.6, 126.4, 63.5, 58.6, 38.9, 33.9. IR (neat): 3340, 3026, 2901, 1602, 1494, 1453, 1029, 999, 972, 744  $\text{cm}^{-1}$ . GC-MS: *tR* 9.36 min (>95%), calcd for  $\text{C}_{10}\text{H}_{12}\text{O}$ : 148.1, found:  $[\text{M}]^+$  148.1.

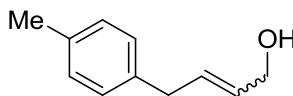
**(*E*)-4-(4-(ethoxycarbonyl)phenyl)-but-2-en-1-ol and (*Z*)-4-(4-(ethoxycarbonyl)phenyl)-but-2-en-1-ol (5.5).**



Following the general procedure given for the synthesis of (*E*)-4-(4-methoxy-phenyl)-but-2-en-1-ol and (*Z*)-4-(4-methoxy-phenyl)-but-2-en-1-ol, (4-ethoxycarbonyl)triethoxysilane (588 mg, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (225 mg, 65%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol.

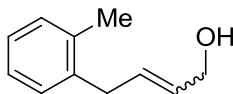
$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  : 7.97 (d,  $J$  = 8.0 Hz, 2H), 7.25 (d,  $J$  = 8.0 Hz, 2H), 5.87-5.68 (m, 2H), 4.38 (q,  $J$  = 7.2 Hz, 2H), 4.32 (d,  $J$  = 6.0 Hz, 0.7H), 4.13 (d,  $J$  = 1.2 Hz, 1.3H), 3.50 (d,  $J$  = 7.2 Hz, 0.7H), 3.45 (d,  $J$  = 6.4 Hz, 1.3H), 1.39 (t,  $J$  = 7.2 Hz, 3H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.8, 145.7, 145.5, 131.3, 130.5, 130.3, 130.2, 130.0, 129.9, 128.8, 129.7, 128.5, 63.6, 61.1, 58.7, 38.8, 33.9, 14.5. IR

(neat): 3399, 2980, 1715, 1610, 1416, 1277, 1104, 1021  $\text{cm}^{-1}$ . GC-MS: *tR* isomer 1: 13.67 min, calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_3$ : 220.1, found:  $[\text{M}]^+$  220.1. *tR* isomer 2: 13.70 min,  $[\text{M}-\text{H}_2\text{O}]^+$  calcd for  $\text{C}_{13}\text{H}_{14}\text{O}_2$ : 202.1, found: 202.1 (peaks overlap, isomer 1 + isomer 2, >95%).

**(E)-4-(4-methyl-phenyl)-but-2-en-1-ol and (Z)-4-(4-methyl-phenyl)-but-2-en-1-ol (5.6).**

Following the general procedure given for the synthesis of (E)-4-(4-methoxyphenyl)-but-2-en-1-ol and (Z)-4-(4-methoxy-phenyl)-but-2-en-1-ol, 4-(triethoxysilyl)toluene (400 mg, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (206 mg, 81%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol. The (*E*) isomer has been previously reported, and the characterization data is consistent with our isolated mixture of olefin isomers.<sup>55</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.13-7.07 (m, 4H), 5.85 (m, 0.7H), 5.75-5.69 (m, 1.3H), 4.32 (d, *J* = 4.8 Hz, 0.7H), 4.13 (d, *J* = 5.6 Hz, 1.3H), 3.42 (d, *J* = 5.2 Hz, 0.7H), 3.36 (d, *J* = 6.8 Hz, 1.3H), 2.34 (s, 3H), 1.28 (t, *J* = 6.0 Hz, 1H). <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  137.4, 137.2, 135.9, 132.08, 131.53, 130.3, 129.5, 129.4, 128.7, 128.4, 63.7, 58.7, 38.4, 33.4, 21.2. IR (neat): 3334, 3019, 2921, 2865, 1514, 1432, 1091, 1021, 1001, 805 cm<sup>-1</sup>. GC-MS: *t*<sub>R</sub> 10.17 min (>95%), calcd for C<sub>11</sub>H<sub>14</sub>O: 162.1, found: [M]<sup>+</sup> 162.1.

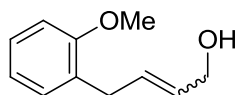
**(E)-4-(2-methyl-phenyl)-but-2-en-1-ol and (Z)-4-(2-methyl-phenyl)-but-2-en-1-ol (5.7).**



Following the general procedure given for the synthesis of (*E*)-4-(4-methoxyphenyl)-but-2-en-1-ol and (*Z*)-4-(4-methoxy-phenyl)-but-2-en-1-ol, 2-(triethoxysilyl)toluene (400 mg, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (204 mg, 80%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.17-7.13 (m, 4H), 5.84 (m, 0.6H), 5.74 (m, 0.4H), 5.7-5.62 (m, 1H), 4.33 (d,  $J = 6.5$  Hz, 0.8H), 4.13 (d,  $J = 5.5$  Hz, 1.2H), 3.42 (d,  $J = 7.0$  Hz, 0.8H), 3.39 (d,  $J = 5.5$  Hz, 1.2H), 2.32 (s, 1.2H), 2.31 (s, 1.8H), 1.32 (bs, 1H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  141.4, 141.1, 139.3, 133.8, 133.5, 133.2, 133.1, 132.3, 132.1, 131.5, 129.4, 129.3, 129.2, 129.1, 66.6, 61.7, 39.1, 34.4, 22.5, 22.3. IR (neat): 3328, 3018, 2924, 1491, 1460, 1001, 972, 744  $\text{cm}^{-1}$ . GC-MS: *tR* isomer 1: 10.27 min, calcd for  $\text{C}_{11}\text{H}_{14}\text{O}$ : 162.1, found:  $[\text{M}]^+$  162.1. *tR* isomer 2: 10.32 min,  $[\text{M}-\text{H}_2\text{O}]^+$  calcd for  $\text{C}_{11}\text{H}_{12}$ : 144.1, found: 144.1 (peaks overlap, isomer 1 + isomer 2 >95%).

**(*E*)-4-(2-methoxy-phenyl)-but-2-en-1-ol and (*Z*)-4-(2-methoxy-phenyl)-but-2-en-1-ol (5.8).**

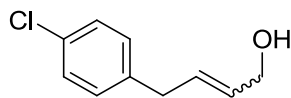


Following the general procedure given for the synthesis of (*E*)-4-(4-methoxyphenyl)-but-2-en-1-ol and (*Z*)-4-(4-methoxy-phenyl)-but-2-en-1-ol, 2-(triethoxysilyl)anisole (510 mg, 1.89 mmol)

and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (229 mg, 82%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.23-7.13 (m, 2H), 6.92-6.81 (m, 2H), 5.88 (m, 0.7H), 5.73-5.67 (m, 1.3H), 4.32 (d,  $J = 5.5$  Hz, 0.6H), 4.12 (d,  $J = 5.5$  Hz, 1.4H), 3.85 (s, 0.9H), 3.84 (s, 2.1H), 3.44 (d,  $J = 5.0$  Hz, 0.6H), 3.39 (d,  $J = 6.5$  Hz, 1.4H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  157.2, 131.2, 131.1, 129.9, 129.8, 129.6, 127.5, 127.4, 120.7, 120.5, 110.4, 110.3, 63.7, 58.5, 55.3, 32.8, 28.3. IR (neat): 3349, 3002, 2923, 1599, 1587, 1492, 1463, 1241, 751  $\text{cm}^{-1}$ . GC-MS: *tR* isomer 1: 11.22 min, calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_2$ : 178.1, found:  $[\text{M}]^+$  178.1. *tR* isomer 2: 11.19 min, calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_2$ : 178.1, found:  $[\text{M}]^+$  178.1 (peaks overlap, isomer 1 + isomer 2 >95%).

**(*E*)-4-(4-chloro-phenyl)-but-2-en-1-ol and (*Z*)-4-(4-chloro-phenyl)-but-2-en-1-ol (5.9).**

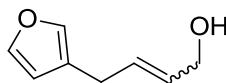


Following the general procedure given for the synthesis of (*E*)-4-(4-methoxyphenyl)-but-2-en-1-ol and (*Z*)-4-(4-methoxy-phenyl)-but-2-en-1-ol, 4-chloro(triethoxysilyl)benzene (518 mg, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (129 mg, 45%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol. The (*Z*) isomer has been previously reported, and the characterization data is consistent with our isolated mixture of olefin isomers.<sup>56</sup>

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.32-7.25 (m, 2H), 7.13-7.06 (m, 2H), 5.86-5.67 (m, 2H), 4.31 (d,  $J = 6.5$  Hz, 0.8H), 4.14 (d,  $J = 5.5$  Hz, 1.2H), 3.42 (d,  $J = 7.0$  Hz, 0.8H), 3.36 (d,  $J = 6.5$  Hz, 1.2H), 1.37 (bs, 1H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  141.6, 141.4, 134.9, 133.9, 133.8, 133.6,

132.9, 132.7, 132.6, 131.6, 131.5, 66.4, 61.5, 40.9, 36.0. IR (neat): 3337, 3024, 2924, 1491, 1406, 1091, 1015, 972, 804  $\text{cm}^{-1}$ . GC-MS: *tR* isomer 1: 11.14 min, calcd for  $\text{C}_{10}\text{H}_{11}\text{ClO}$ : 182.1, found:  $[\text{M}]^+$  182.1. *tR* isomer 2: 11.16 min,  $[\text{M}-\text{H}_2\text{O}]^+$  calcd for  $\text{C}_{10}\text{H}_9\text{Cl}$ : 164.1, found: 164.1 (peaks overlap, isomer 1 + isomer 2 >95%).

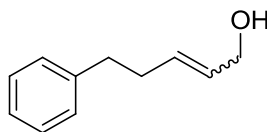
**(*E*)-4-(3-furanyl)-2-buten-1-ol and (*Z*)-4-(3-furanyl)-2-buten-1-ol (5.10).**



Following the general procedure given for the synthesis of (*E*)-4-(4-methoxy-phenyl)-but-2-en-1-ol and (*Z*)-4-(4-methoxy-phenyl)-but-2-en-1-ol, benzyltrietoxysilane (0.4 mL, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (147 mg, 68%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.37 (t,  $J = 2$  Hz, 1H), 7.23 (m, 0.1H), 6.28 (m, 1H), 5.82 (m, 0.7H), 5.77-5.68 (m, 1.3H), 4.29 (d,  $J = 5.2$  Hz, 0.6H), 4.14 (d,  $J = 5.6$  Hz, 1.4H), 3.24 (d,  $J = 5.6$  Hz, 0.6H), 3.19 (d,  $J = 2.4$  Hz, 1.4H), 1.34 (bs, 1H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  143.3, 143.1, 139.4, 139.2, 130.8, 130.4, 129.7, 123.2, 111.3, 111.0, 63.7, 58.7, 27.9, 23.3. IR (neat): 3353, 2923, 1653, 1378, 1132, 1083, 1022, 960  $\text{cm}^{-1}$ . GC-MS: *tR* 7.73 min (>95%), calcd for  $\text{C}_8\text{H}_{10}\text{O}_2$ : 138.1, found:  $[\text{M}]^+$  138.1.

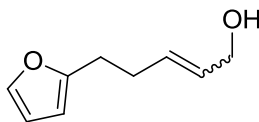
**(2*E*)-5-phenyl-2-penten-1-ol and (2*Z*)-5-phenyl-2-penten-1-ol (5.11).**



Following the general procedure given for the synthesis of (E)-4-(4-methoxy-phenyl)-but-2-en-1-ol and (Z)-4-(4-methoxy-phenyl)-but-2-en-1-ol, benzyltriethoxysilane (481 mg, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (178 mg, 70%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol. The (E) and (Z) isomers have been individually synthesized and reported and the characterization data is consistent with our isolated mixture of olefin isomers.<sup>57</sup>

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.34-7.29 (m, 2H), 7.24-7.20 (m, 3H), 5.79-5.66 (m, 1.7H), 5.61 (m, 0.3H), 4.92 (d, *J* = 5.5 Hz, 1.7H), 4.03 (d, *J* = 6.0 Hz, 0.3H), 2.75-2.70 (m, 2H), 2.45-2.38 (m, 2H). <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>): δ 141.6, 141.4, 132.1, 131.4, 129.5, 129.4, 128.5, 128.3, 128.2, 126.0, 125.8, 63.5, 58.2, 35.6, 35.5, 33.9, 29.2. IR (neat): 3339, 3026, 2925, 1603, 1496, 1453, 1083, 1000, 970 cm<sup>-1</sup>. GC-MS: *tR* isomer 1: 9.96 min, calcd for C<sub>11</sub>H<sub>14</sub>O: 162.1, found: [M]<sup>+</sup> 162.1. *tR* isomer 2: 10.05 min, calcd for C<sub>11</sub>H<sub>14</sub>O: 162.1, found: [M]<sup>+</sup> 162.1 (peaks overlap, isomer 1 + isomer 2 >95%).

**(2E)-5-(2-furanyl)-2-penten-1-ol and (2Z)-5-(2-furanyl)-2-penten-1-ol (5.12).**



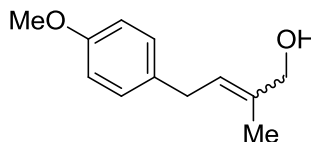
Following the general procedure given for the synthesis of (E)-4-(4-methoxy-phenyl)-but-2-en-

1-ol and (Z)-4-(4-methoxy-phenyl)-but-2-en-1-ol, benzyltriethoxysilane (322 mg, 1.89 mmol) and butadiene monoepoxide (110 mg, 1.57 mmol) were transformed into the title alcohol (213 mg, 89%). Chromatography eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol.

The (*E*) isomer has been previously reported, and the characterization data is consistent with our isolated mixture of olefin isomers.<sup>58</sup>

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.32 (m, 0.1H), 7.31 (m, 0.9H), 6.29 (m, 1H), 6.0 (m, 1H), 5.76-5.68 (m, 1.8H), 5.66 (m, 0.2H), 4.12 (d, *J* = 7 Hz, 0.2H), 4.09 (d, *J* = 4.5 Hz, 1.8H), 2.74-2.70 (m, 2H), 2.46-2.26 (m, 2H), 1.73 (bs, 0.1H), 1.47 (bs, 0.9H). <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>): δ 158.4, 144.1, 143.9, 134.6, 134.2, 132.9, 132.6, 113.2, 113.1, 108.4, 108.0, 66.6, 61.4, 33.6, 30.9, 30.7, 29.0. IR (neat): 3333, 2920, 2854, 1652, 1506, 1009, 970 cm<sup>-1</sup>. GC-MS: *t*R 8.38 min (>95%), calcd for C<sub>9</sub>H<sub>12</sub>O<sub>2</sub>: 152.1, found: [M]<sup>+</sup> 152.2. GC-MS: *t*R 7.73 min (>95%), calcd for C<sub>9</sub>H<sub>12</sub>O<sub>2</sub>: 152.1, found: [M]<sup>+</sup> 152.2.

**(2*E*)-4-(4-methoxyphenyl)-2-methyl-2-buten-1-ol and (2*Z*)-4-(4-methoxyphenyl)-2-methyl-2-buten-1-ol (5.13).**

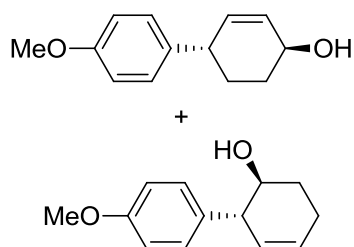


The product was purified by silica gel chromatography (eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol) to afford the title compound (227 mg, 82% yield).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.12-7.09 (m, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.61 (t, *J* = 7.5 Hz, 0.5H), 5.50 (t, *J* = 8.0 Hz, 0.5H), 4.25 (s, 1H), 4.06 (s, 1H), 3.38 (s, 3H), 3.36 (t, *J* = 7.5 Hz, 2H),

1.86 (s, 1.5H), 1.79 (s, 1.5H), 1.45 (bs, 0.5H), 1.38 (bs, 0.5H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  160.9, 138.4, 138.0, 136.0, 132.2, 132.1, 130.3, 128.1, 117.0, 116.9, 71.8, 64.6, 58.3, 36.0, 35.9, 24.4, 16.8. IR (film): 3358, 2913, 2835, 1610, 1511, 1464, 1246, 1176, 1035  $\text{cm}^{-1}$ . GC-MS: *tR* isomer 1: 12.15 min, calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_2$ : 192.1, found:  $[\text{M}]^+$  192.2. *tR* isomer 2: 12.32 min, calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_2$ : 192.1, found:  $[\text{M}]^+$  192.2 (peaks overlap, isomer 1 + isomer 2 >95%). The (*E*) isomer has been previously reported, and the characterization data is consistent with our isolated mixture of olefin isomers.<sup>53</sup>

**4-(4-methoxyphenyl)-2-cyclohexen-1-ol and 6-(4-methoxyphenyl)-2-cyclohexen-1-ol (5.14).**

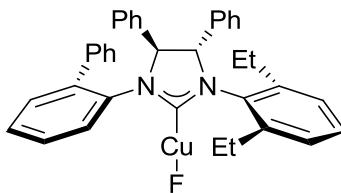


The product was purified by silica gel chromatography (eluent: 400:20:20:1 hexanes/acetone/dichloromethane/methanol) to afford the title compound (256mg, 81% yield).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.19 (m, 0.4H), 7.13-7.09 (m, 1.6H), 6.96-6.89 (m, 2H), 5.92-5.80 (m, 1.8H), 5.57 (m, 0.2H), 4.34 (m, 0.8H), 3.81 (s, 1H), 3.80 (s, 2H), 3.72 (m, 0.2H), 3.39 (m, 0.8H), 3.27 (m, 0.2), 2.28 (m, 0.4H), 2.19-1.99 (m, 2.8H), 1.73 (m, 0.2H), 1.62-1.51 (m, 1.6H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  158.8, 158.3, 137.7, 135.2, 133.2, 131.6, 129.6, 128.9, 128.7, 127.8, 73.9, 66.7, 55.5, 50.8, 41.3, 32.0, 30.8, 29.6, 24.8. IR (neat): 3372, 3022, 2934, 1610, 1508, 1302, 1245, 1176, 1109, 828  $\text{cm}^{-1}$ . GC-MS: *tR* isomer 1: 13.22 min, calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_2$ : 204.1, found:  $[\text{M}]^+$  204.2. *tR* isomer 2: 12.84 min, calcd for  $\text{C}_{13}\text{H}_{16}\text{O}_2$ : 204.1,

found: [M]<sup>+</sup> 204.2 (peaks overlap, isomer 1 + isomer 2 >95%).

### Chiral (NHC)CuF, 5.15

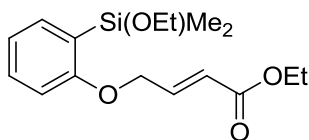


In a glovebox, an oven-dried round-bottom flask was charged with chiral imidazolium salt<sup>38</sup> (1.0 g, 1.7 mmol). Fresh CuCl (0.165 g, 1.7 mmol), NaOt-Bu (0.161 g, 1.7 mmol), and THF (9.5mL) were added to this round-bottom flask. The resulting suspension was stirred at room temperature for 4 h, then filtered over celite and concentrated *in vacuo*. The (NHC)CuCl complex was obtained as a light brown powder (1.0 g, 85% yield). <sup>1</sup>H NMR (400 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ 1.00 (t, *J* = 7.6 Hz, 3H), 1.50 (t, *J* = 7.6 Hz, 3H), 1.93 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.48 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.84 (dq, *J* = 15.2, 7.6 Hz, 1H), 2.93 (dq, *J* = 15.2, 7.6 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 5.11(d, *J* = 9.6 Hz, 1H), 6.46 (d, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 6.4 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 3H), 7.11-7.30 (12H, m), 7.51-7.53(m, 2H), 7.60-7.63 (m, 2H), 7.67-7.70 (m, 4H). In a glovebox, an oven-dried round-bottom flask was charged (NHC)CuCl complex (1.0 g, 1.4 mmol) and NaOt-Bu (0.139 g, 1.4 mmol). THF (8 mL) was added to the round-bottom flask. The resulting suspension was stirred at room temperature for 2 h, then filtered over celite and concentrated *in vacuo*. The (NHC)CuOt-Bu complex was obtained as a tan powder (0.97 g, 95% yield). In a glovebox, (NHC)CuOt-Bu (0.97 g, 1.3 mmol) and toluene (12 mL) were added to a round-bottom flask equipped with a Teflon-coated stirbar. The flask was sealed with a rubber septum and removed from the glovebox. Triethylamine tris(hydrofluoride) (0.068 mL, 0.42 mmol) was added via syringe. The resulting white suspension was stirred for 6 h and the solvent was removed via reduced pressure. In the glovebox, the white solid was suspended in pentane (6

mL), filtered, and washed with pentane (6 mL) to afford the title compound (**5.15**) as a pale yellow powder (0.68 g, 76 %).

$^1\text{H}$  NMR (400 MHz, THF  $d_8$ ):  $\delta$  1.03 (t,  $J = 7.6$  Hz, 3H), 1.40 (t,  $J = 7.6$  Hz, 3H), 1.90 (dq,  $J = 15.2, 7.6$  Hz, 1H), 2.54 (dq,  $J = 15.2, 7.6$  Hz, 1H), 2.83 (dq,  $J = 15.2, 7.6$  Hz, 1H), 2.98 (dq,  $J = 15.2, 7.6$  Hz, 1H), 5.03 (d,  $J = 10.0$  Hz, 1H), 5.07 (d,  $J = 9.6$  Hz, 1H), 6.64 (d,  $J = 7.6$  Hz, 2H), 7.02 (d,  $J = 6.4$  Hz, 1H), 7.06 (t,  $J = 7.6$  Hz, 3H), 7.10-7.31 (12H, m), 7.68(bs, 5H), 7.73 (d,  $J = 7.6$  Hz, 1H).

**(E)-ethyl 4-(2-(ethoxydimethylsilyl)phenoxy)but-2-enoate, 5.16**



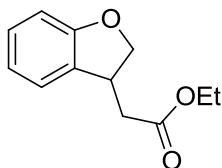
A solution of *n*-BuLi (1.6 M in pentane, 8.2 mL, 13.18 mmol) was added dropwise to a stirring solution of the allyloxy-2-bromobenzene (1.5 g, 5.26 mmol) in Et<sub>2</sub>O (20 mL) at to -78 °C. After 1 h, the solution was added via cannula to a stirring solution of dichlorodimethylsilane (1.6 mL, 13.19 mmol) in Et<sub>2</sub>O (20 mL) at -78 °C. After 3 h, the reaction mixture was warmed to 0 °C and triethylamine (2.4 mL, 17.15 mmol) followed by ethanol (1.0 mL, 17.15 mmol) was added dropwise. The reaction mixture was poured into pentane (50 mL) and filtered through silica gel. The concentrated material was then subjected to bulb-to-bulb distillation to afford 1.8 g (58% yield) of the desired product.  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  0.39 (s, 6H), 1.19 (t,  $J = 7.0$ , 3H), 3.71 (q,  $J = 7.0$ , 2H), 4.10 (dt,  $J = 5.0$  and 1.5 Hz, 2H), 5.03 (dq,  $J = 10.5$  and 1.5 Hz, 1H), 5.25 (dq,  $J = 17.0$  and 1.5 Hz, 1H), 5.71 (m, 1H), 6.53 (dt,  $J = 8.0$  and 0.5 Hz, 1H), 6.97 (td,  $J = 7.0$  and 1.0 Hz, 1H), 7.20 (m, 1H), 7.75 (dd,  $J = 7.0$  and 2.0 Hz, 1H). To a mixture of (2-



(allyloxy)phenyl)(ethoxy)dimethylsilane (0.57 g, 2.4 mmol) and ethyl acrylate (2.45 g, 24.2 mmol) in dichloromethane (8 mL) was added Grubb's second generation catalyst (70 mg, 0.08 mmol). The resulting mixture was refluxed for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. Purification by flash chromatography (hexane:ether) afforded the desired cross-metathesis product, **5.16**, 291 mg (40% yield) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.41 (s, 6H), 1.23 (t,  $J = 7.0$ , 3H), 1.31 (t,  $J = 7.0$  Hz, 3H), 3.76 (q,  $J = 7.0$ , 2H), 4.23 (q,  $J = 7.0$  Hz, 2H), 4.73 (dd,  $J = 4.0$  and 2.0 Hz, 2H), 6.23 (dt,  $J = 15.5$  and 2.0 Hz, 1H), 6.79 (d,  $J = 8.0$  Hz, 1H), 7.02 (td,  $J = 7.0$  and 1.0 Hz, 1H), 7.10 (dt,  $J = 15.5$  and 4.0 Hz, 1H), 7.36 (m, 1H), 7.53 (dd,  $J = 7.0$  and 2.0 Hz, 1H).

#### Ethyl 2-(2,3-dihydrobenzofuran-2-yl)acetate, **5.17**



In a glove box, a 20-mL scintillation vial equipped with a Teflon-coated stir bar and a rubber septum was charged with (NHC)CuF **5.15** (3 mg, 0.0044 mmol) and anhydrous THF (0.5 mL). The vial was then taken out of the glove box and sealed with electrical tape. Organosilane (28 mg, 0.095 mmol) was added to the solution by syringe and the mixture was stirred for 1 d at 50 °C. The reaction was applied to a silica gel column (eluent 20:1 hexanes: ether). Purification afforded the product 19 mg (98%) as a colorless oil. Data was comparable to that available in the literature.<sup>59</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.29 (t,  $J = 7.0$  Hz, 3H), 2.59 (dd,  $J = 16.0, 9.5$  Hz, 1H), 2.80 (dd,  $J = 16.0, 5.5$  Hz, 1H), 3.88 (m, 1H), 4.19 (q,  $J = 7.0$  Hz, 2H), 4.27 (dd,  $J = 9.5, 6.0$  Hz, 1H), 4.76 (t,  $J = 9.0$  Hz, 1H), 6.81 (m, 1H), 6.80 (d,  $J = 7.0$  Hz, 1H), 6.87 (td,  $J = 7.0, 1.0$  Hz, 1H), 7.13-7.19 (m, 2H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.2, 38.3, 39.5, 60.7, 77.2, 109.7, 120.5, 124.2, 128.6, 129.1, 159.8, 171.8.

## 5.6 References

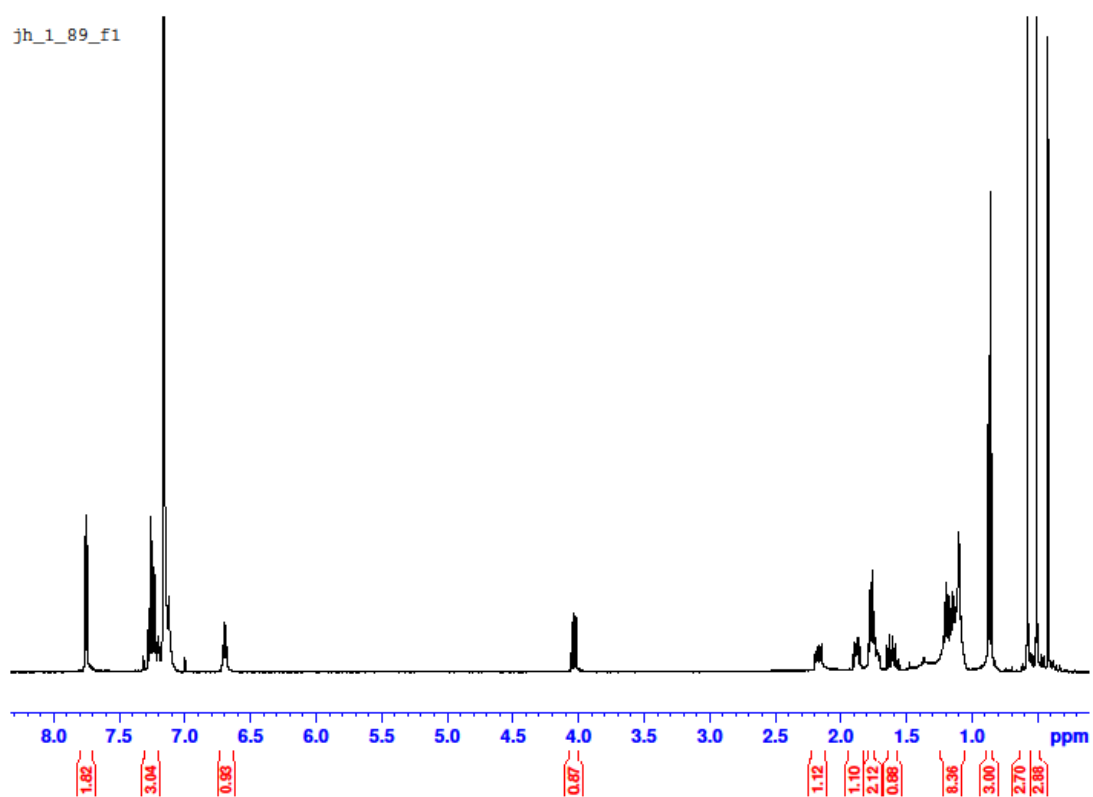
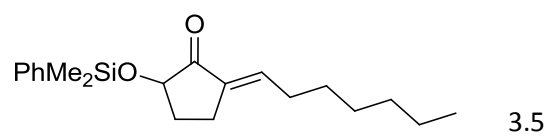
- (1) I. Ojima, Z. L., J. Zhu in *The Chemistry of Organic Silicon Compounds*; New York: Wiley, 1998; Vol. 2.
- (2) Denmark, S. E.; Amishiro, N. *J. Org. Chem.* 2003, 68, 6997.
- (3) Denmark, S. E.; Regen, C. S. *Acc. Chem. Res.* 2008, 41, 1486.
- (4) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* 2004, 126, 4865.
- (5) Denmark, S. E.; Wehrli, D. *Org. Lett.* 2000, 2, 565.
- (6) Denmark, S. E.; Wehrli, D.; Choi, J. Y. *Org. Lett.* 2000, 2, 2491.
- (7) Seganish, W. M.; DeShong, P. *Org. Lett.* 2006, 8, 3951.
- (8) Shukla, K. H.; DeShong, P. *J. Org. Chem.* 2008, 73, 6283.
- (9) Shukla, K. H.; DeShong, P. *J. Org. Chem.* 2008, 73, 6283.
- (10) Kuninobu, Y.; Ishii, E.; Takai, K. *Angew. Chem. Int. Ed.* 2007, 46, 3296.
- (11) Huang, T. S.; Meng, Y.; Venkatraman, S.; Wang, D.; Li, C. J. *J. Am. Chem. Soc.* 2001, 123, 7451.
- (12) Huang, T. S.; Venkatraman, S.; Meng, Y.; Nguyen, T. V.; Kort, D.; Wang, D.; Ding, R.; Li, C. J. *Pure Appl. Chem.* 2001, 73, 1315.
- (13) Koike, T.; Du, X. L.; Mori, A.; Osakada, K. *Synlett* 2002, 301.
- (14) Nakao, Y.; Chen, J.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W.-L.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* 2007, 129, 9137.
- (15) Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* 2002, 4, 667.

- (16) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* 2002, 58, 91.
- (17) Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* 2002, 5, 97.
- (18) Rose, M.; Baxter, M.; Brereton, N.; Baskaran, C. *Food Additives and Contaminants Part a-Chemistry Analysis Control Exposure & Risk Assessment* 2010, 27, 1380.
- (19) Venkatraman, S.; Li, C. J. *Tetrahedron Lett.* 2001, 42, 781.
- (20) Venkatraman, S.; Meng, Y.; Li, C. J. *Tetrahedron Lett.* 2001, 42, 4459.
- (21) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* 2004, 126, 4876.
- (22) Ito, H.; Arimoto, K.; Sensui, H.; Hosomi, A. *Tetrahedron Lett.* 1997, 38, 3977.
- (23) Nishihara, Y.; Kato, T.; Ando, J.; Mori, A.; Hiyama, T. *Chem. Lett.* 2001, 950.
- (24) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J. Org. Chem.* 2000, 65, 1780.
- (25) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* 2002, 67, 8450.
- (26) Franz, A. K.; Woerpel, K. A. *J. Am. Chem. Soc.* 1999, 121, 949.
- (27) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* 2001, 3, 3811.
- (28) Dubinina, G. G.; Ogikubo, J.; Vicic, D. A. *Organometallics* 2008, 27, 6233.
- (29) Dubinina, G. G.; Furutachi, H.; Vicic, D. A. *J. Am. Chem. Soc.* 2008, 130, 8600.
- (30) Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J. I. *Org. Lett.* 2004, 6, 3695.
- (31) Nishihara, Y.; Ikegashira, K.; Toriyama, F.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* 2000, 73, 985.
- (32) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* 2005, 127, 4138.
- (33) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* 2006, 128, 13052.

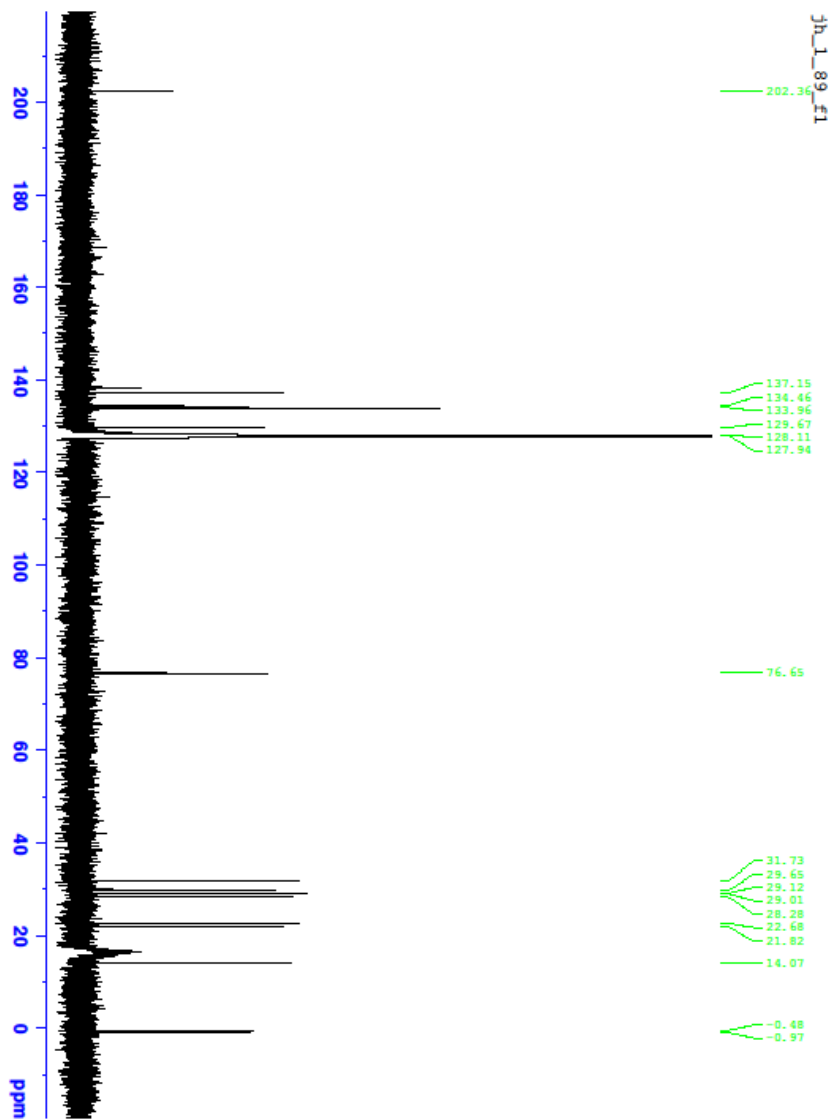
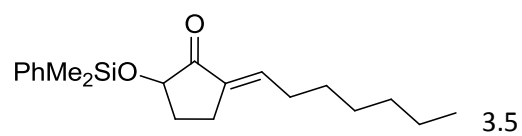
- (34) Pilcher, A. S.; DeShong, P. *Journal of Organic Chemistry* 1996, *61*, 6901.
- (35) Hanamoto, T.; Kobayashi, T.; Kondo, M. *Synlett* 2001, 446.
- (36) Sun, H. R.; DiMagno, S. G. *J. Am. Chem. Soc.* 2005, *127*, 2050.
- (37) Gulliver, D. J.; Levason, W.; Webster, M. *Inorganica Chimica Acta-Articles* 1981, *52*, 153.
- (38) Lee, K.-S.; Hoveyda, A. H. *J. Org. Chem.* 2009, *74*, 4455.
- (39) Herron, J. R.; Ball, Z. T. *J. Am. Chem. Soc.* 2008, *130*, 16486.
- (40) Diez-Gonzalez, S.; Nolan, S. P. *Synlett* 2007, 2158.
- (41) Ledoux, N.; Allaert, B.; Pattyn, S.; Vander Mierde, H.; Vercaemst, C.; Verpoort, F. *Chem. Eur. J.* 2006, *12*, 4654.
- (42) Laitar, D. S., Ph.D. Thesis. Massachusetts Institute of Technology, Cambridge, MA, 2006.
- (43) Larock, R. C.; Ilkka, S. J. *Tetrahedron Lett.* 1986, *27*, 2211.
- (44) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* 2004, *23*, 3369.
- (45) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* 2011, *2*, 649.
- (46) Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* 2007, *46*, 1097.
- (47) Kacprzynski, M. A.; Kazane, S. A.; May, T. L.; Hoveyda, A. H. *Org. Lett.* 2007, *9*, 3187.
- (48) Alexakis, A.; Backvall, J. E.; Krause, N.; Pamies, O.; Dieguez, M. *Chem. Rev.* 2008, *108*, 2796.
- (49) Manoso, A. S.; Ahn, C.; Soheili, A.; Handy, C. J.; Correia, R.; Seganish, W. M.; DeShong, P. *Journal of Organic Chemistry* 2004, *69*, 8305.
- (50) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* 2004, *126*, 13942.
- (51) Annis, G. D.; Ley, S. V.; Self, C. R.; Sivaramakrishnan, R. *Journal of the Chemical Society-Perkin Transactions 1* 1981, 270.

- (52) Chiellini, G.; Nguyen, N. H.; Apriletti, J. W.; Baxter, J. D.; Scanlan, T. S. *Biorg. Med. Chem.* 2002, 10, 333.
- (53) Taber, D. F.; Sikkander, M. I.; Berry, J. F.; Frankowski, K. J. *Journal of Organic Chemistry* 2008, 73, 1605.
- (54) Manolikakes, G.; Hernandez, C. M.; Schade, M. A.; Metzger, A.; Knochel, P. *Journal of Organic Chemistry* 2008, 73, 8422.
- (55) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *Journal of Organic Chemistry* 1983, 48, 2449.
- (56) Morgan, T. K.; Wohl, R. A.; Lumma, W. C.; Wan, C. N.; Davey, D. D.; Gomez, R. P.; Marisca, A. J.; Briggs, M.; Sullivan, M. E.; Wong, S. S. *Journal of Medicinal Chemistry* 1986, 29, 1398.
- (57) Kim, I. S.; Dong, G. R.; Jung, Y. H. *Journal of Organic Chemistry* 2007, 72, 5424.
- (58) Trost, B. M.; Zhang, T. *Organic Letters* 2006, 8, 6007.
- (59) Burns, P. A.; Taylor, N. J.; Rodrigo, R. *Canadian Journal of Chemistry-Revue Canadienne De Chimie* 1994, 72, 42.

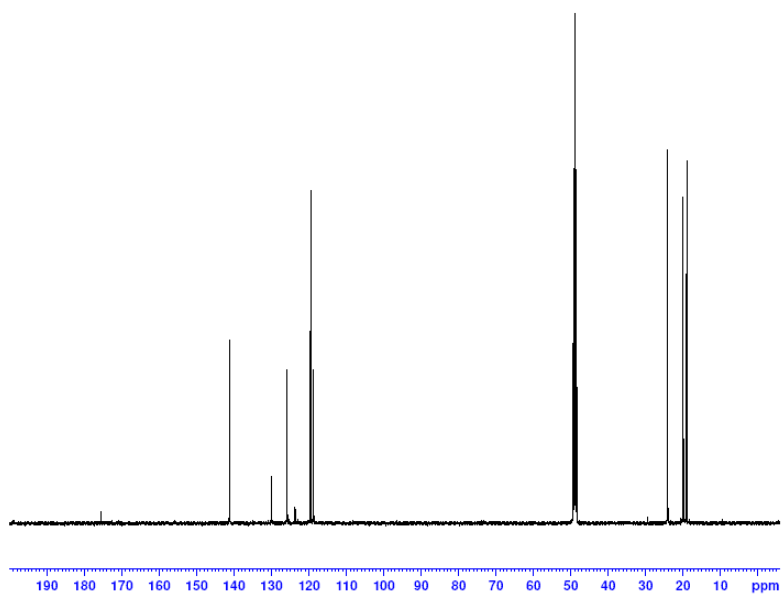
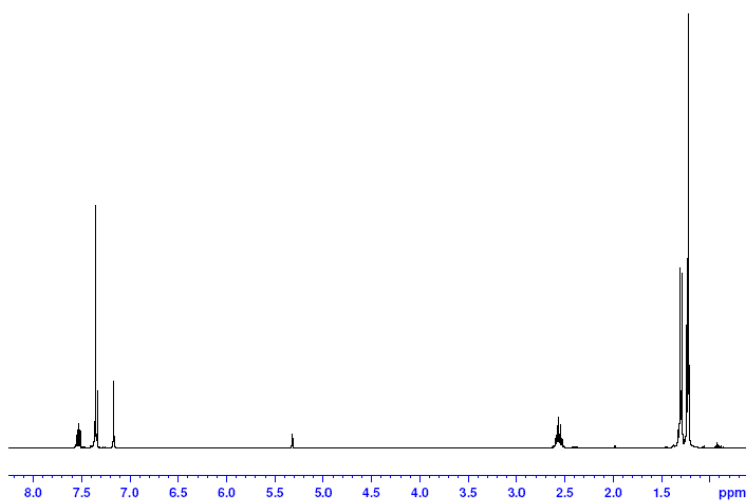
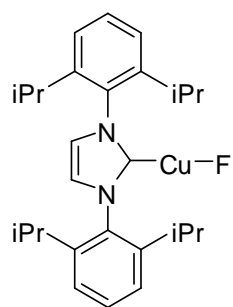
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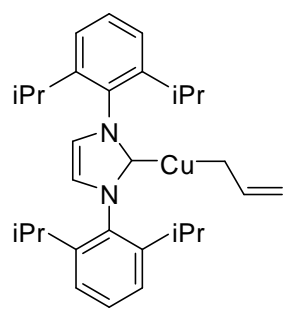




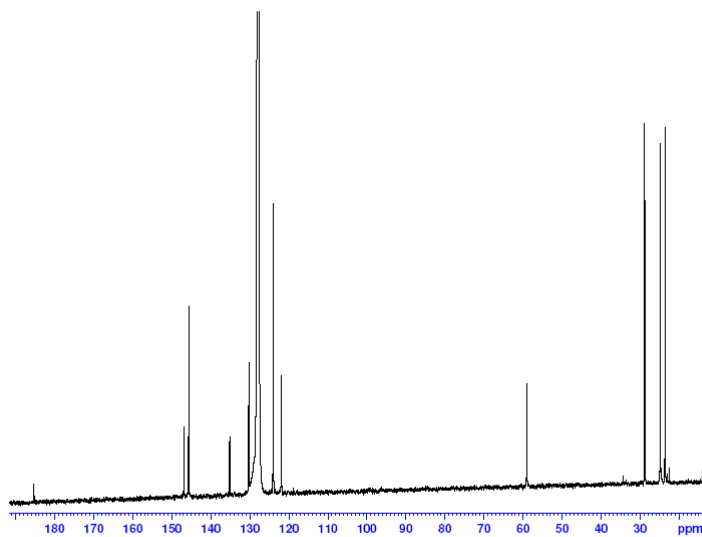
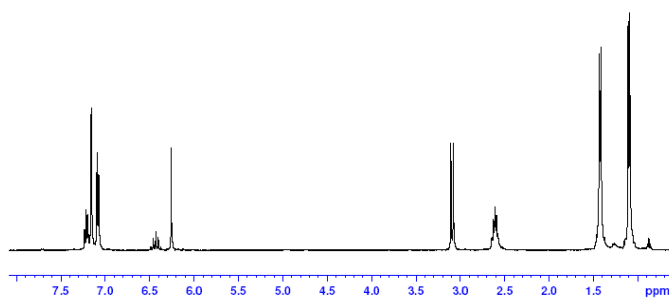


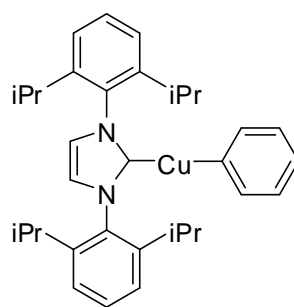
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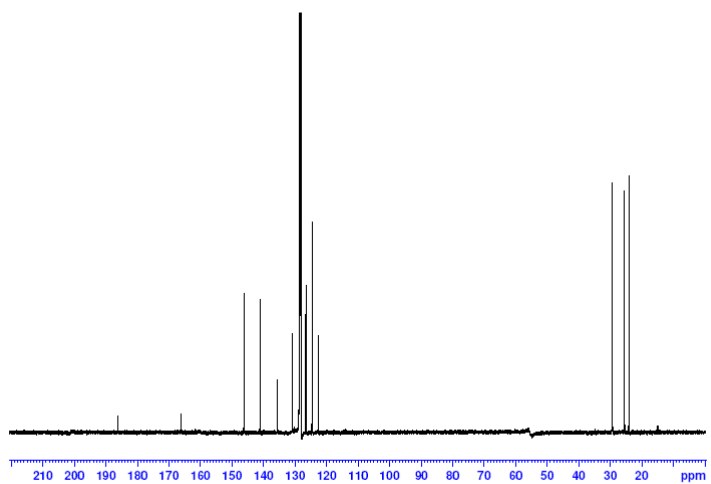
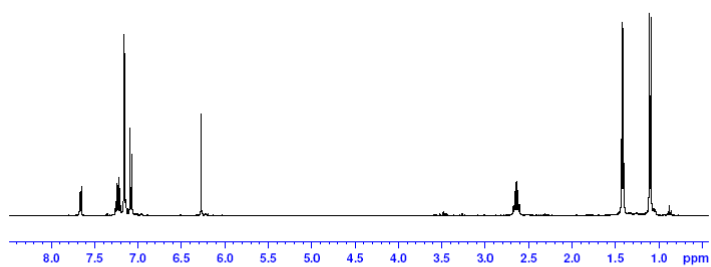


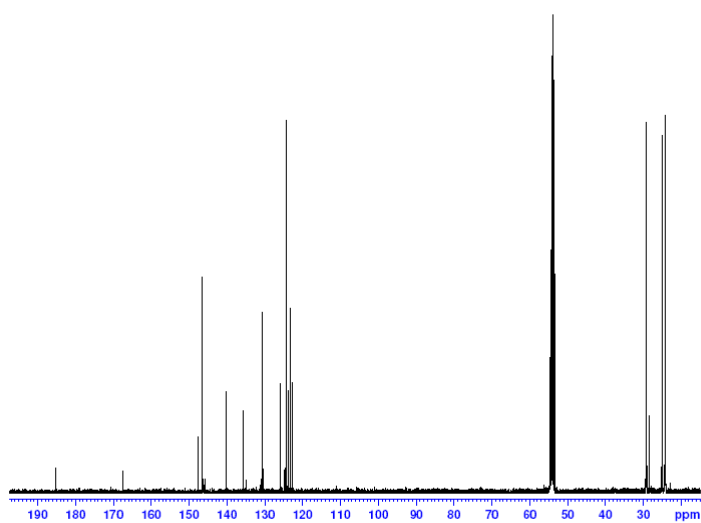
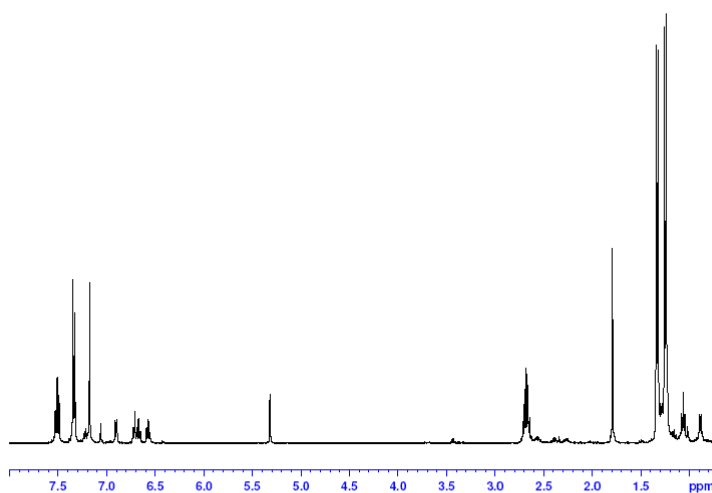
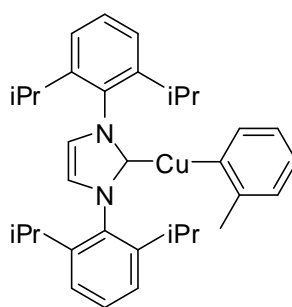
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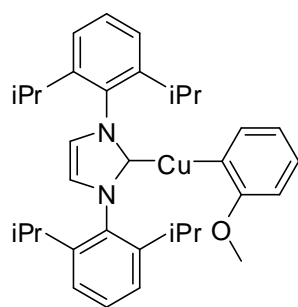




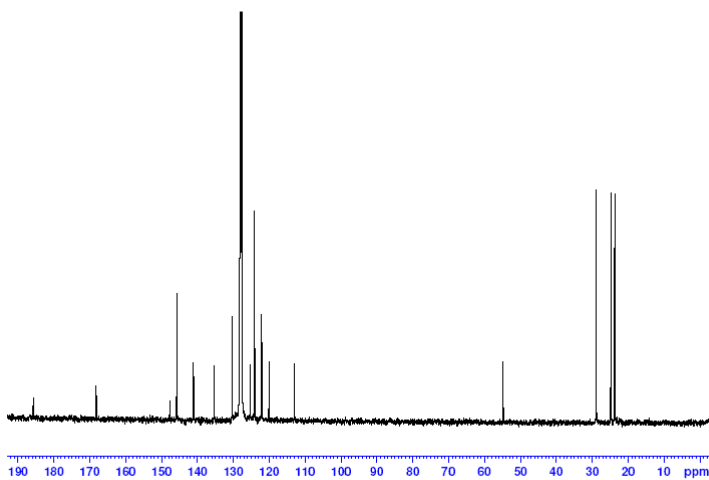
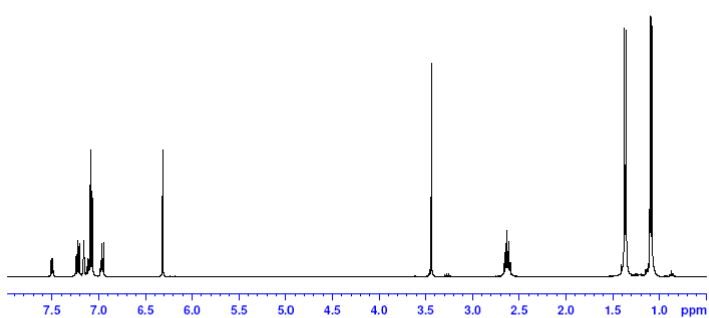
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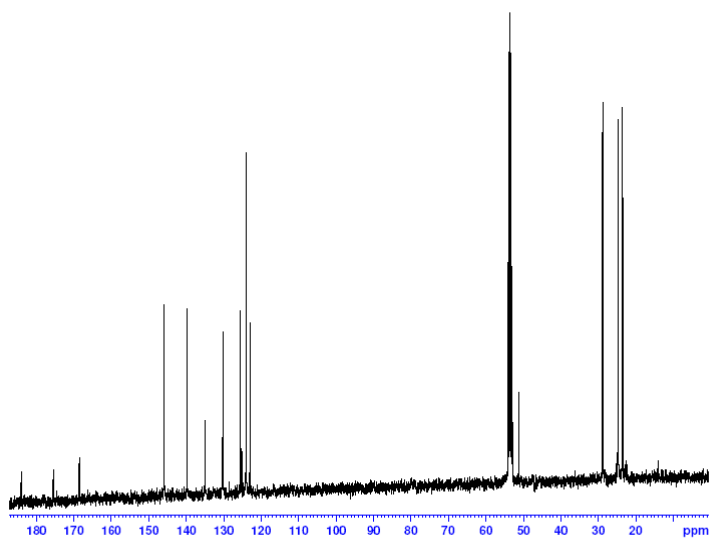
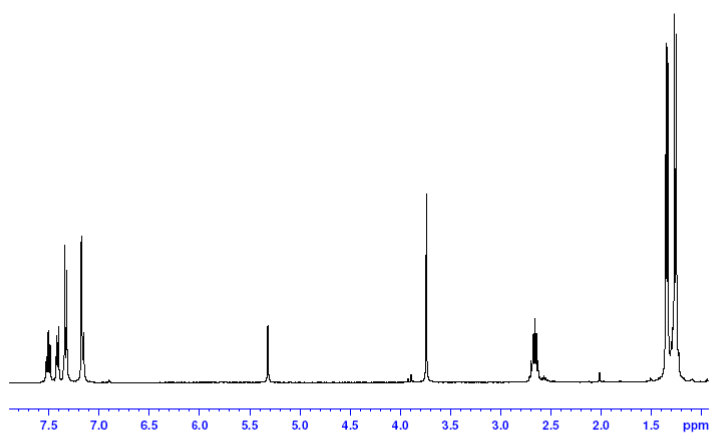
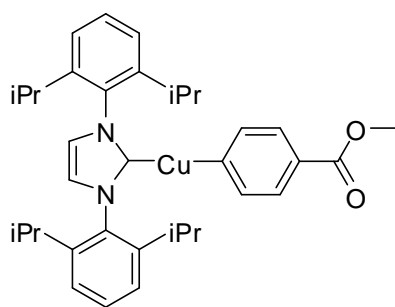




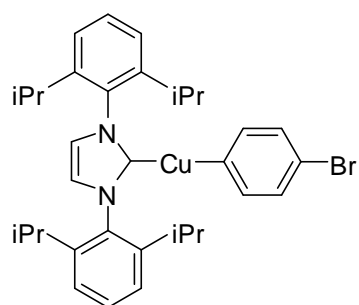


4.9

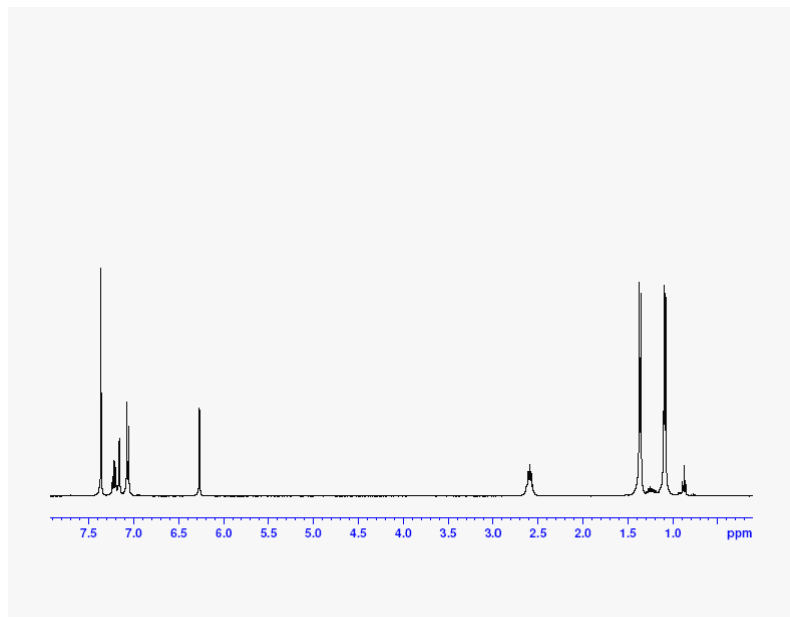




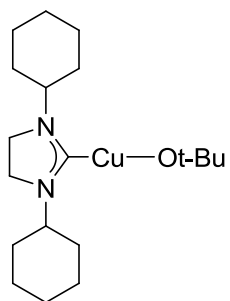




4.13

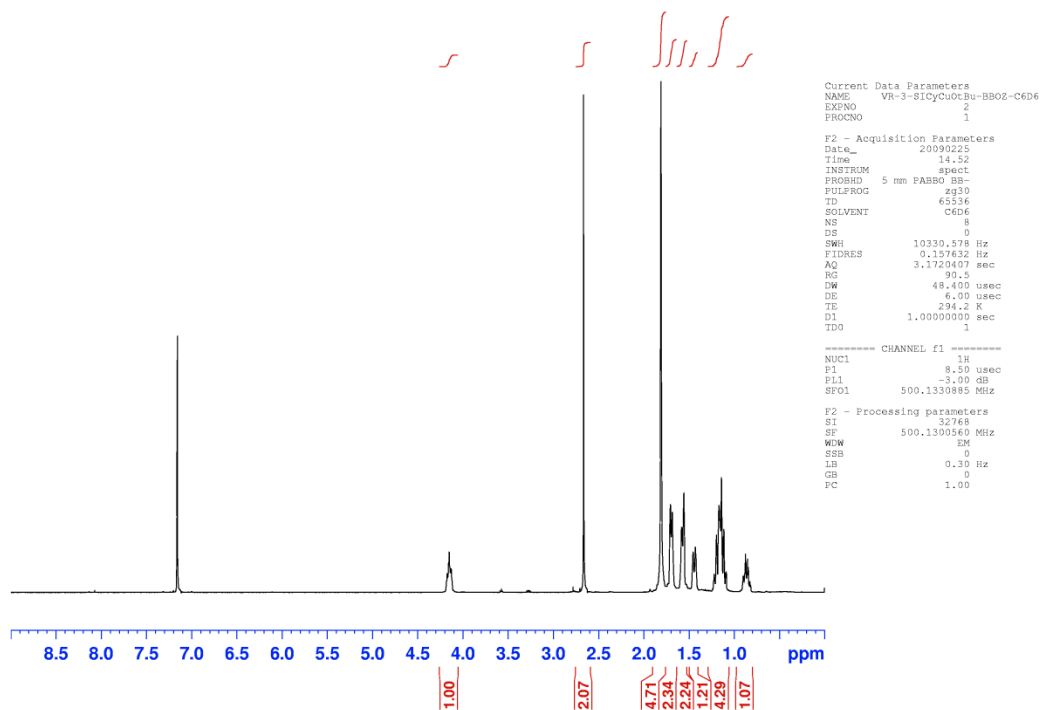


## **Appendix C. Selected Spectra for Chapter 5**

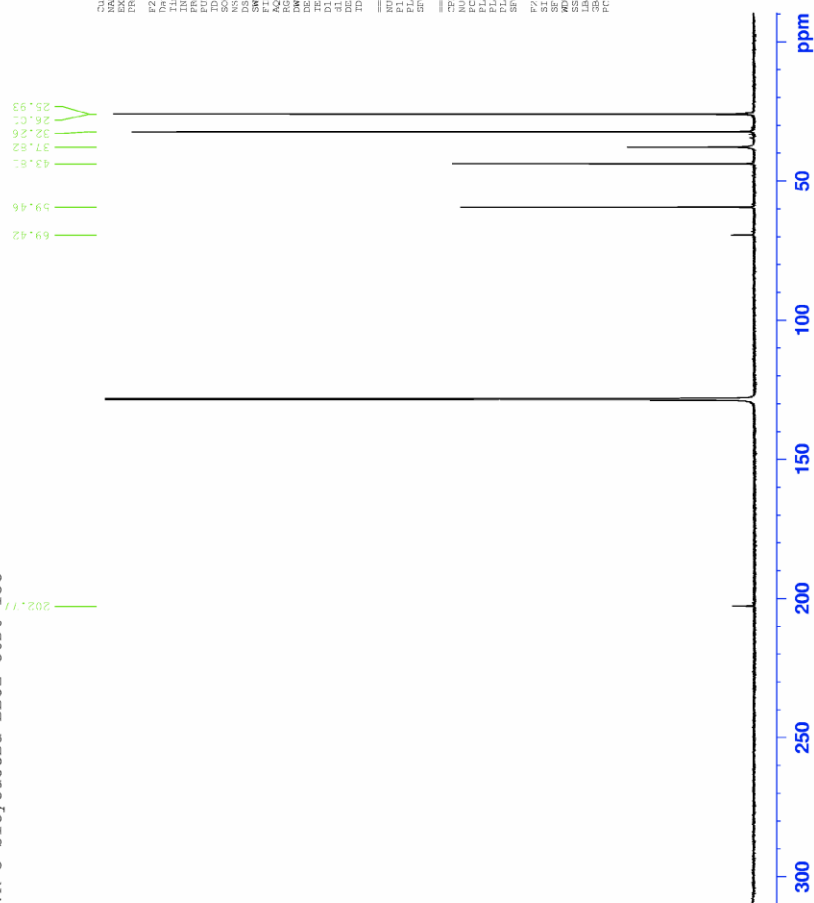


5.1

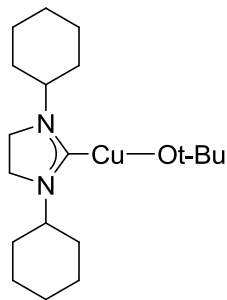
VR-3-SiCyCuOtBu-BBOZ-C6D6



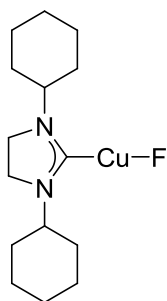
VR-3-SiCyCuOtBu-BBOZ-C6D6-13C



Current Data Parameters  
 NAME VR-3-SiCyCuOtBu-BBOZ-C6D6-13C  
 PROCO 1  
 P2 - Acquisition Parameters  
 Date 2/11/2022  
 Time 14:57  
 INSTRUM spect  
 PROBRD 5 mm FANNO BB-  
 PULPROG zgpg30  
 ID PULPROG 20070  
 SCAVENT 7000  
 DS 0  
 SS 0  
 SMO 40322.502 Hz  
 FIDRES 0.3333333 Hz  
 AQ 0.3999984 sec  
 RG 5792.6  
 DE 2.0000000 usec  
 DB 6.0000000 usec  
 PC 1.0000000 Ksec  
 DI 0.03000000 sec  
 d11 0.03000000 sec  
 d12 0.03000000 sec  
 DELTA 0.03999998 sec  
 TD 32768  
 ===== CHANNEL F1 13C =====  
 NUCL1 13C  
 P1 9.30 usec  
 PL1 0.00 dB  
 PC1 125.776590 MHz  
 ===== CHANNEL F2 =====  
 CPDPRG2 waltz16  
 NUCL2 1H  
 P2 80.00 usec  
 PL2 -3.00 dB  
 PL12 3.00 dB  
 PL13 3.00 dB  
 PL14 3.00 dB  
 SFO2 500.1320013 MHz  
 P2 - Processing Parameters  
 SI 32768  
 SF 131.072 MHz  
 DSF 125.7777778 MHz  
 SSF 3.00 Hz  
 GB 0  
 PC 1.200

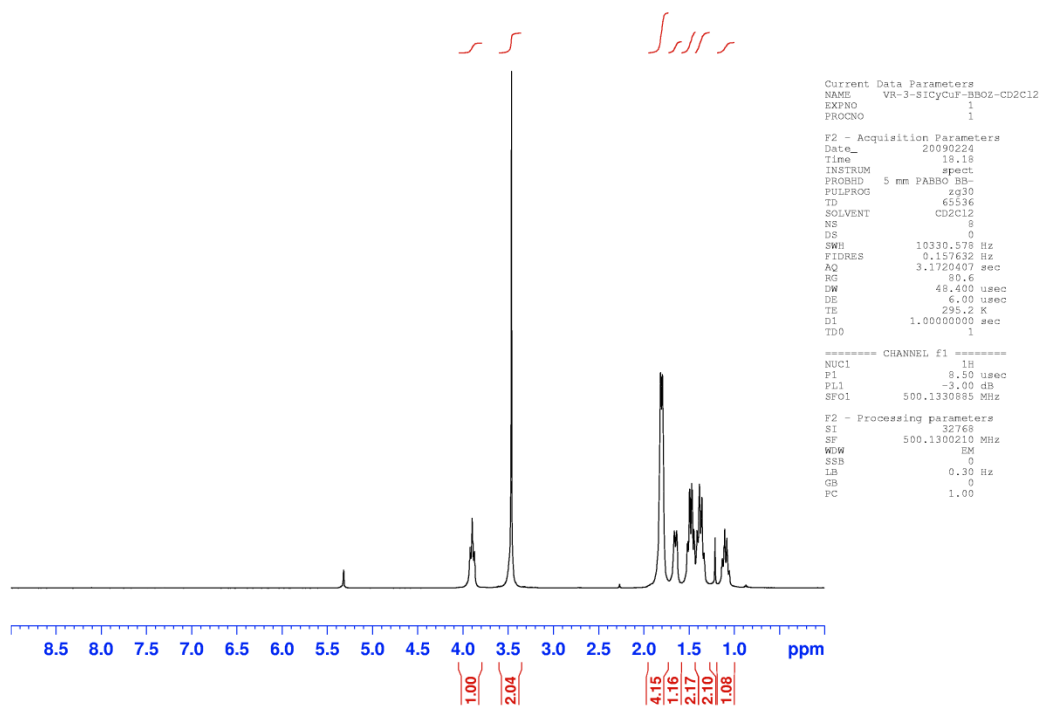


5.1



5.2

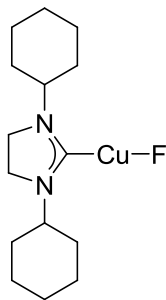
VR-3-SiCyCuF-BBOZ-CD2Cl2



VR-3-SiCyCuF-BBOZ-CD2Cl2-13C



Current Data Parameters  
 Name VR-3-SiCyCuF-BBOZ-CD2Cl2-13C  
 EXNO 1  
 PROCNO 1  
 F2 - Acquisition Parameters  
 Date\_ 20090224  
 Time 18.23  
 INSTRUM spect  
 PROCNO 1  
 FIDRES 0.100445  
 ID 80640  
 NAME VR-3-SiCyCuF-BBOZ-CD2Cl2-13C  
 NS 712  
 DS 0  
 AS 46522.50 Hz  
 SFO1 125.765690 MHz  
 P1 0.500132 sec  
 PT 0.999984 sec  
 AG 0.999984 sec  
 RG 1233.2  
 IN 16.00 usec  
 DE 16.00 usec  
 TE 283.2 K  
 FID 1.600000 sec  
 SFO2 500.132725 MHz  
 DELTA 2.000000 sec  
 TD 65536  
 TDC -0.000  
 ===== CHANNEL f1 =====  
 NUC1 13C  
 P1 0.500132 sec  
 PL1 0.00 dB  
 SFO1 125.765690 MHz  
 ===== CHANNEL f2 =====  
 CHH462 wa-1z16  
 NUC2 1H  
 P2 0.000000 sec  
 PL2 0.00 dB  
 SFO2 500.132725 MHz  
 PL12 -3.50 dB  
 PL13 -3.50 dB  
 PL14 -3.50 dB  
 PL15 -3.50 dB  
 F2 - Processing parameters  
 SI 32768  
 SF 125.767719 MHz  
 GB 0  
 ME 0  
 AS 0  
 DS 0  
 SS 0  
 TB 0  
 FC 1.50

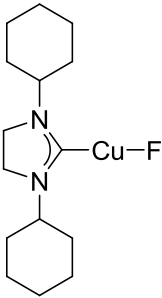


5.2

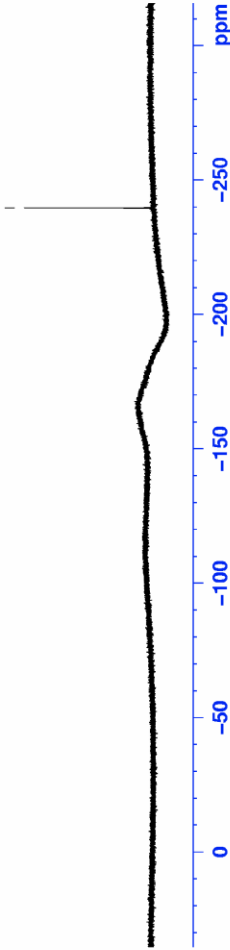
VR-3-63-19F-BBOZ-crude-CD2Cl2

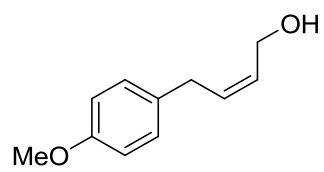
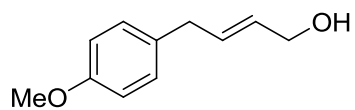
-239.707

Current Data Parameters  
NAME VR-3-63-19F-BBOZ-crude-CD2Cl2  
EXPNO 3  
PROCNO 1  
F2 - Acquisition Parameters  
Date\_ 20110717  
Time 10.14  
INSTRUM spect  
PROBHD 5 mm PAS3  
PULPROG zgpg30  
TD 65536  
FIDRES 0.250007 Hz  
AQ 1.3999955 sec  
RG 327.68  
DE 5.50 usec  
TE 300.2 K  
D1 3.0000000 sec  
TD0 128  
----- CHANNEL F1 -----  
NUC1 19F  
P1 1.50 usec  
PL1 3.00 dB  
SFO1 470.326451 MHz  
F2 Processing parameters  
SI 32768  
SF 470.326451 MHz  
WDW EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.00

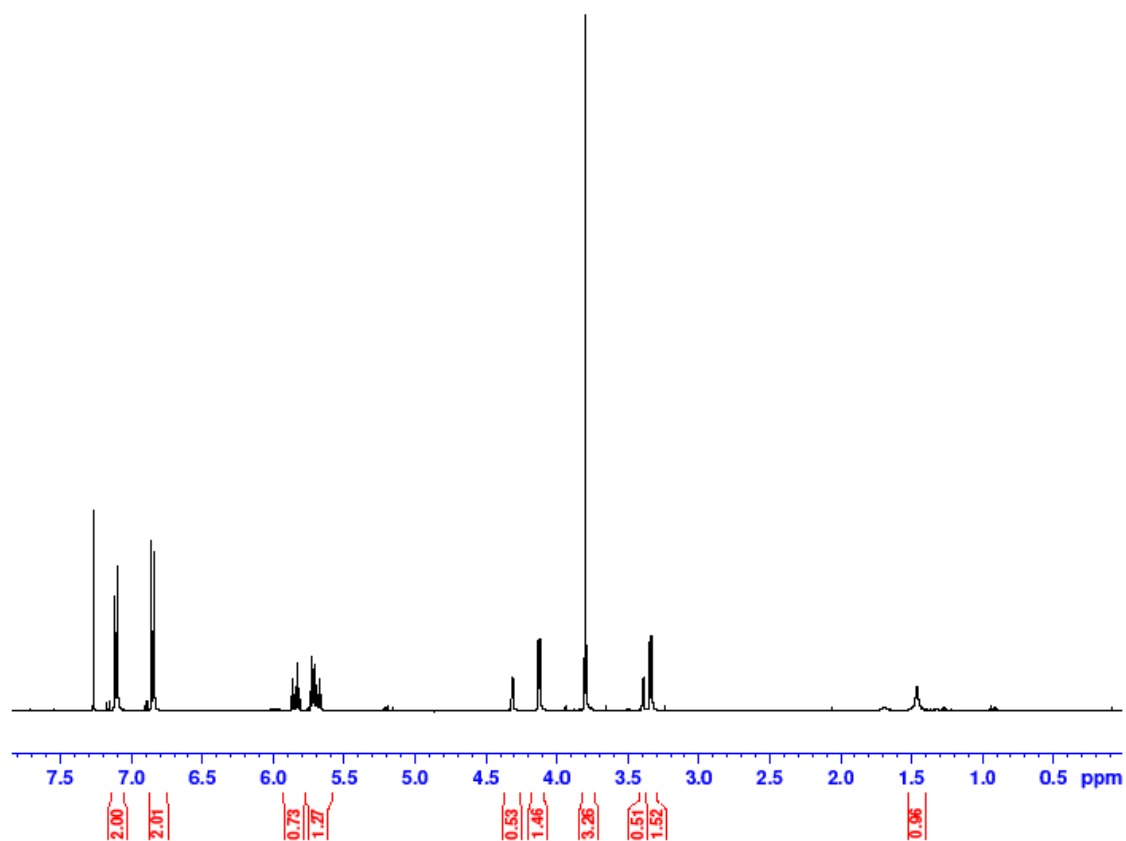


5.2

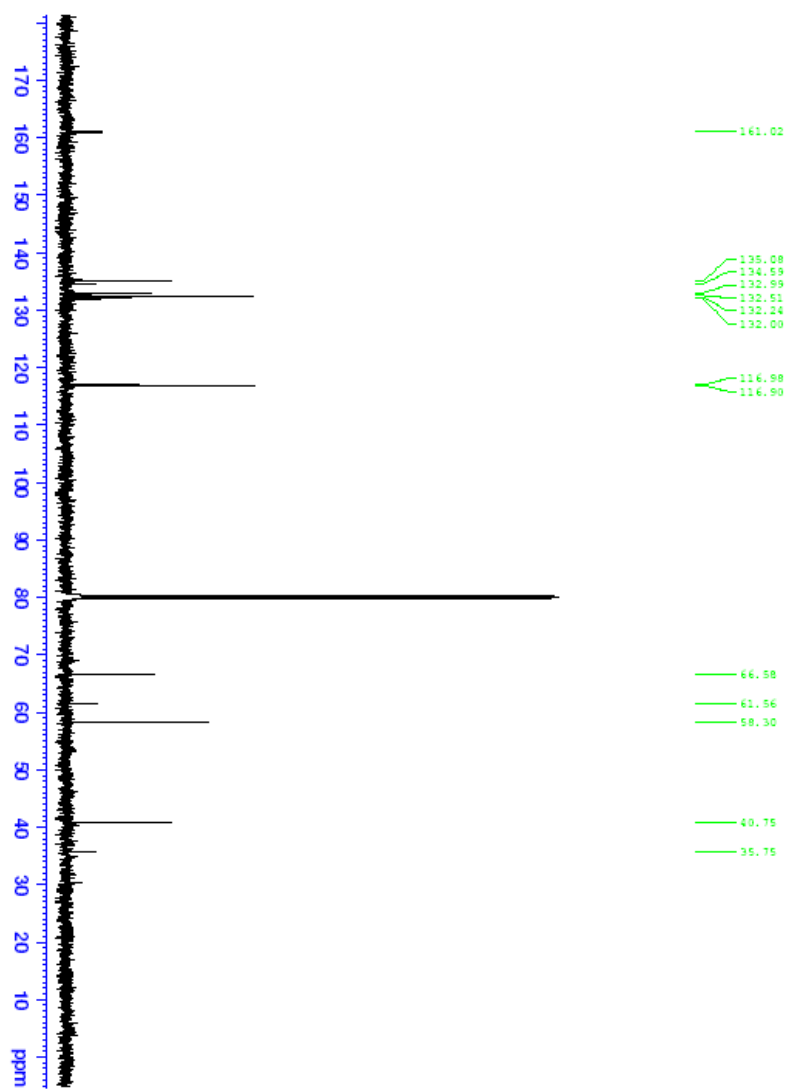
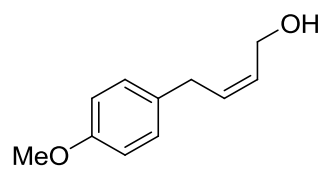
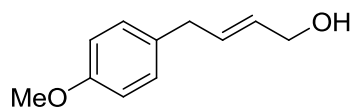


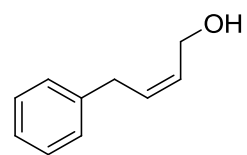
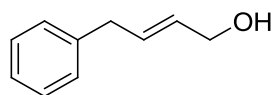


5.4

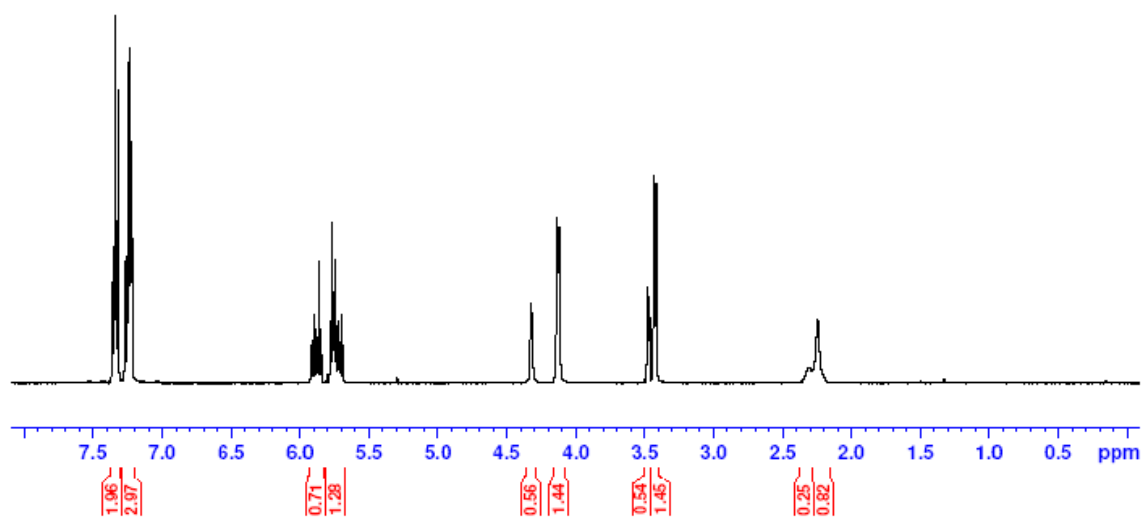


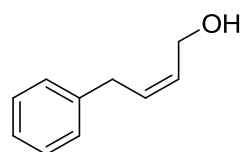
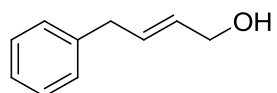




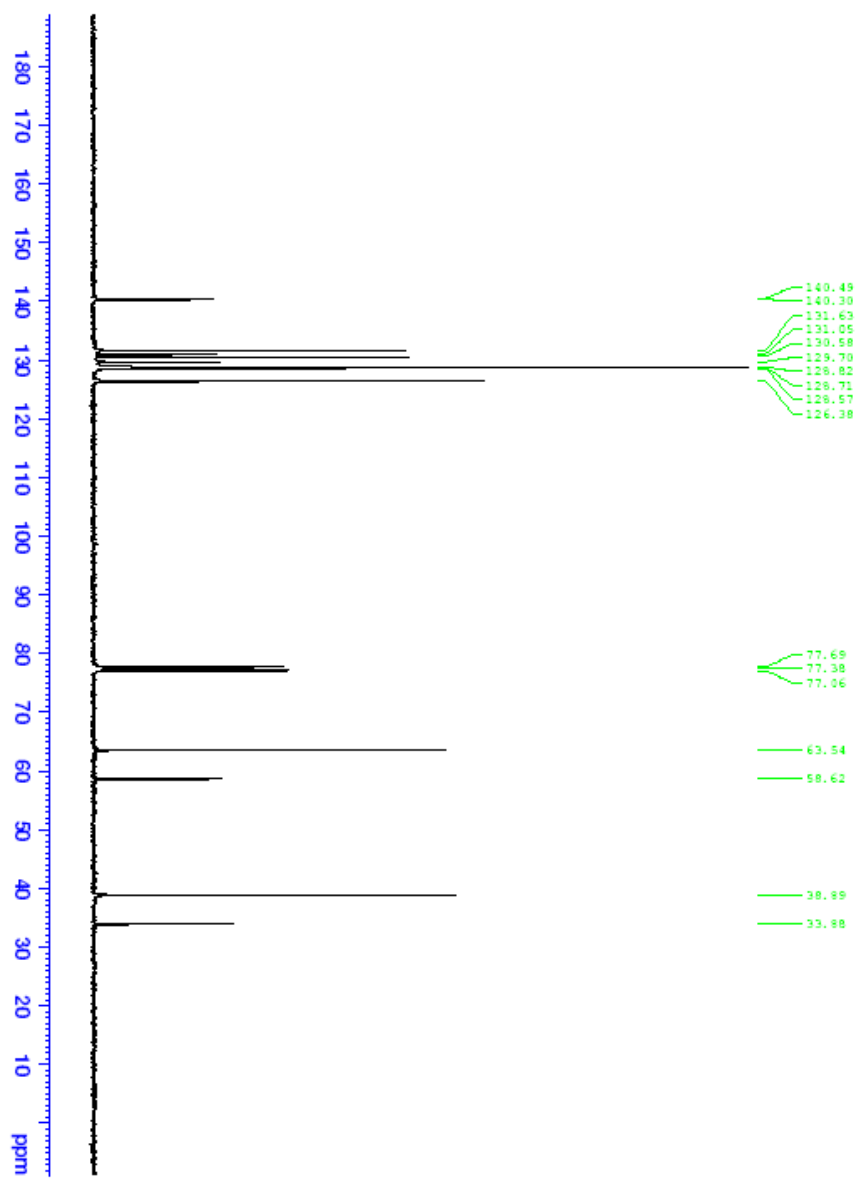


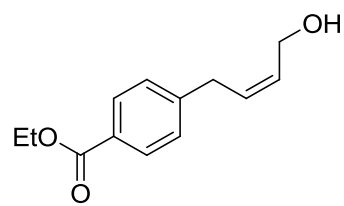
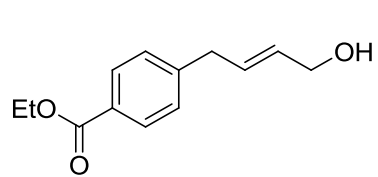
5.3



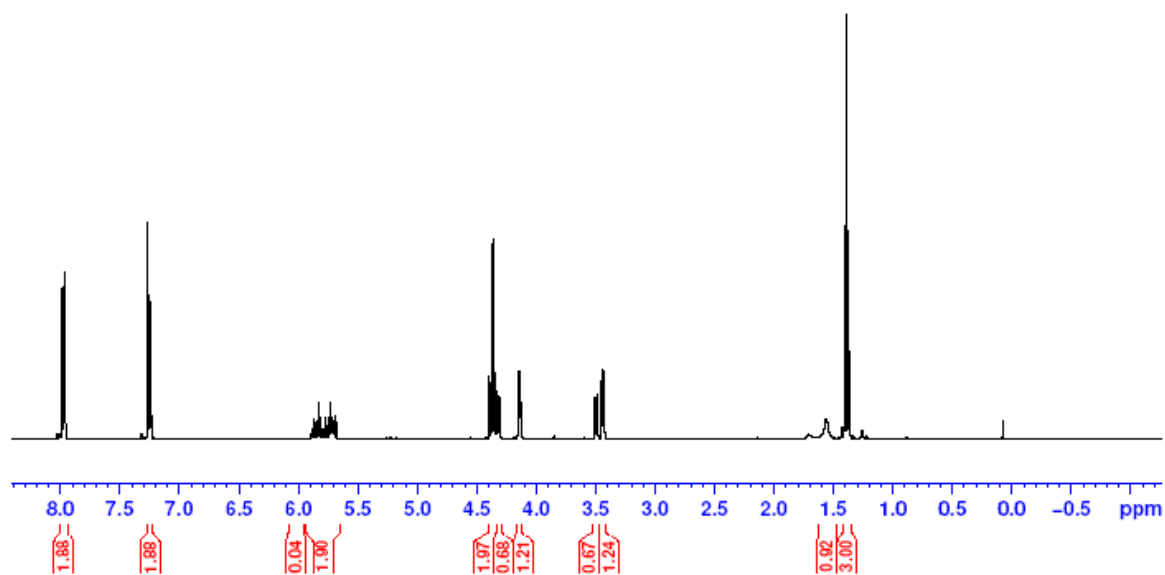


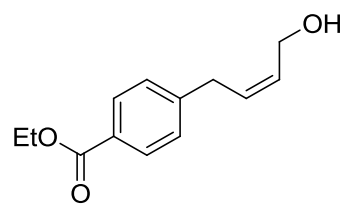
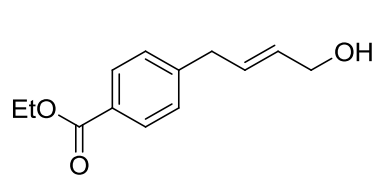
5.3



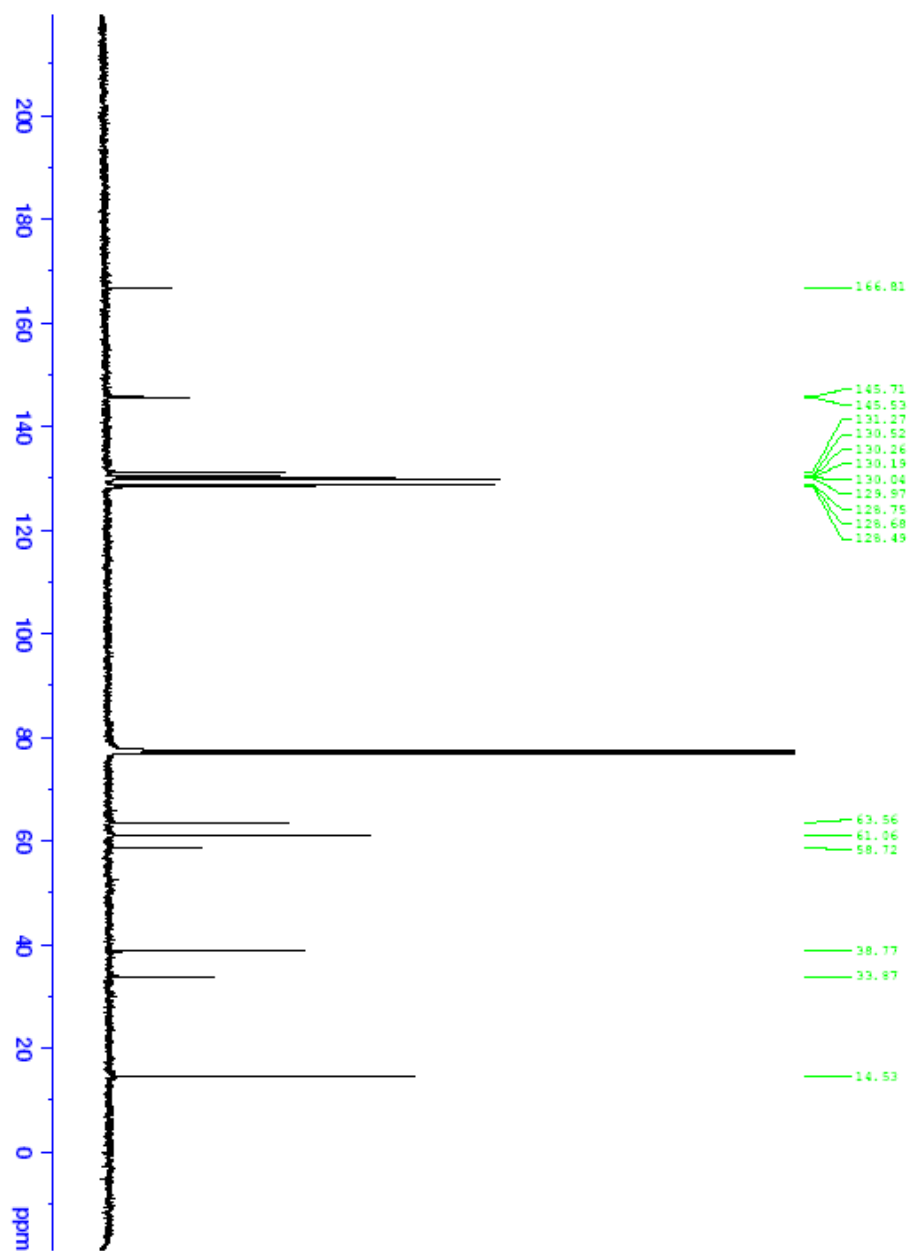


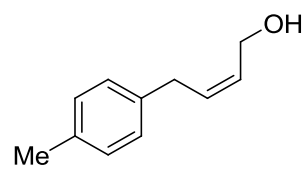
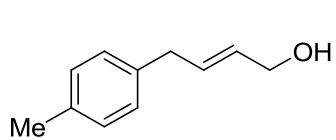
5.5



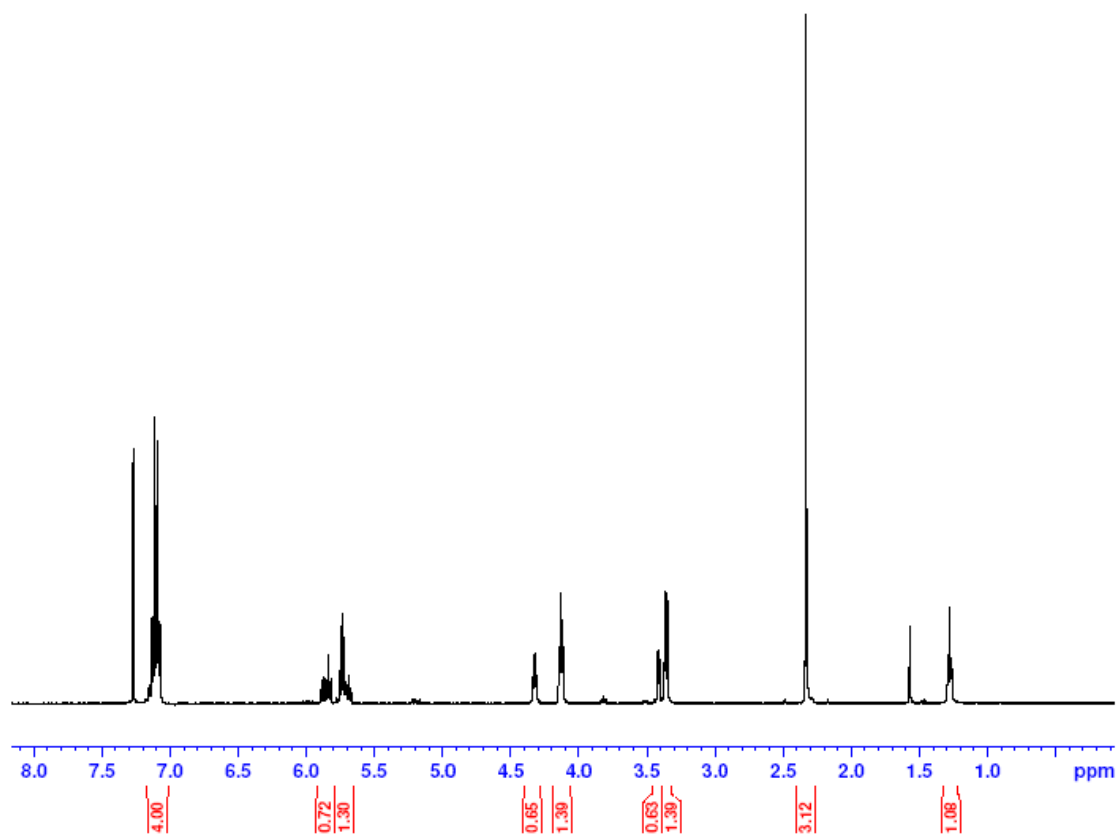


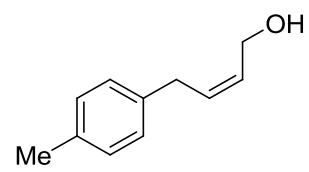
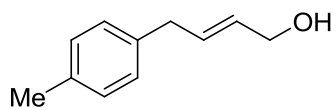
5.5



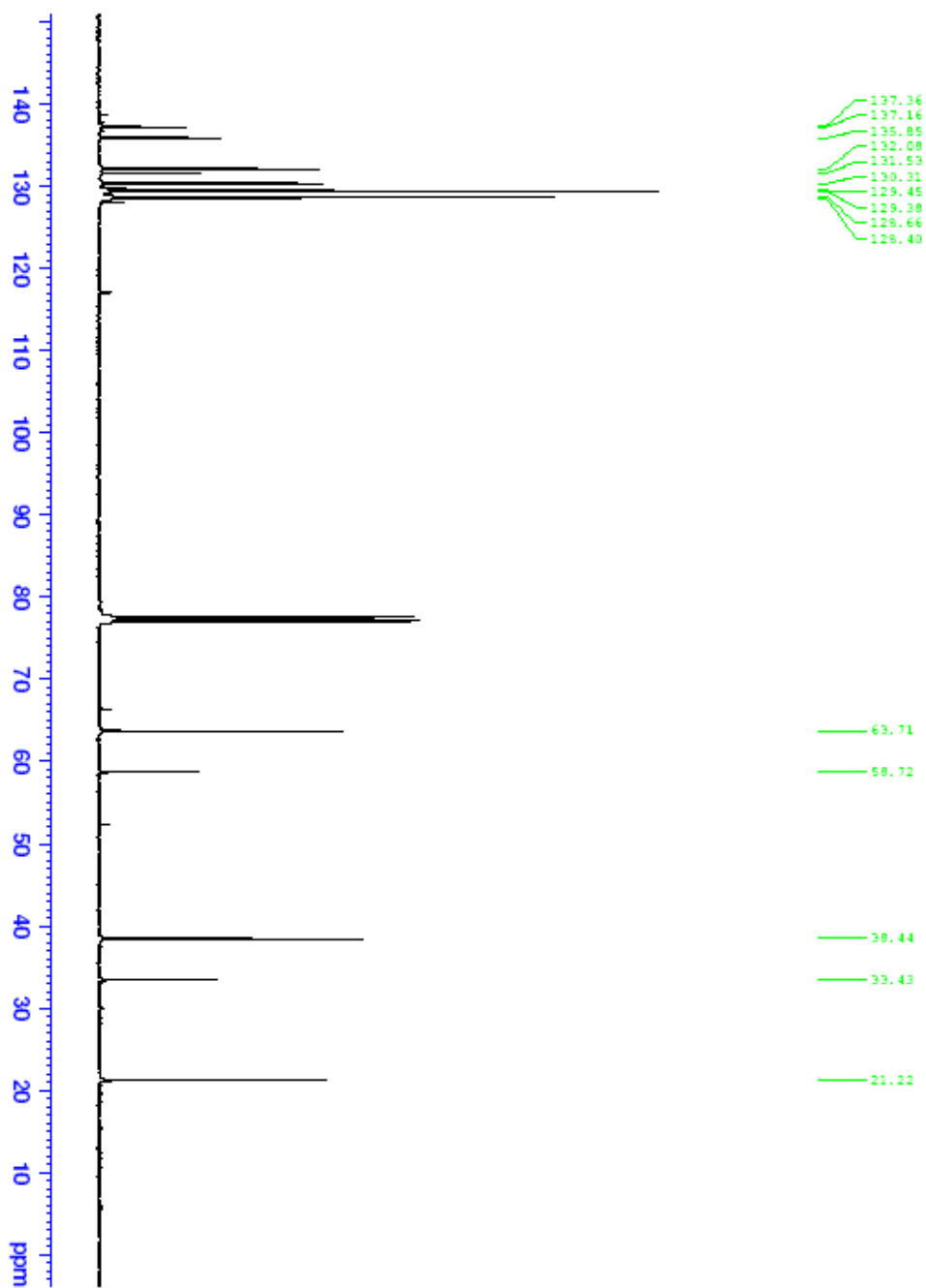


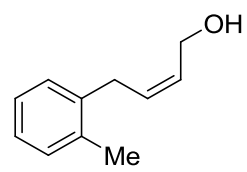
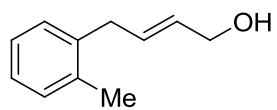
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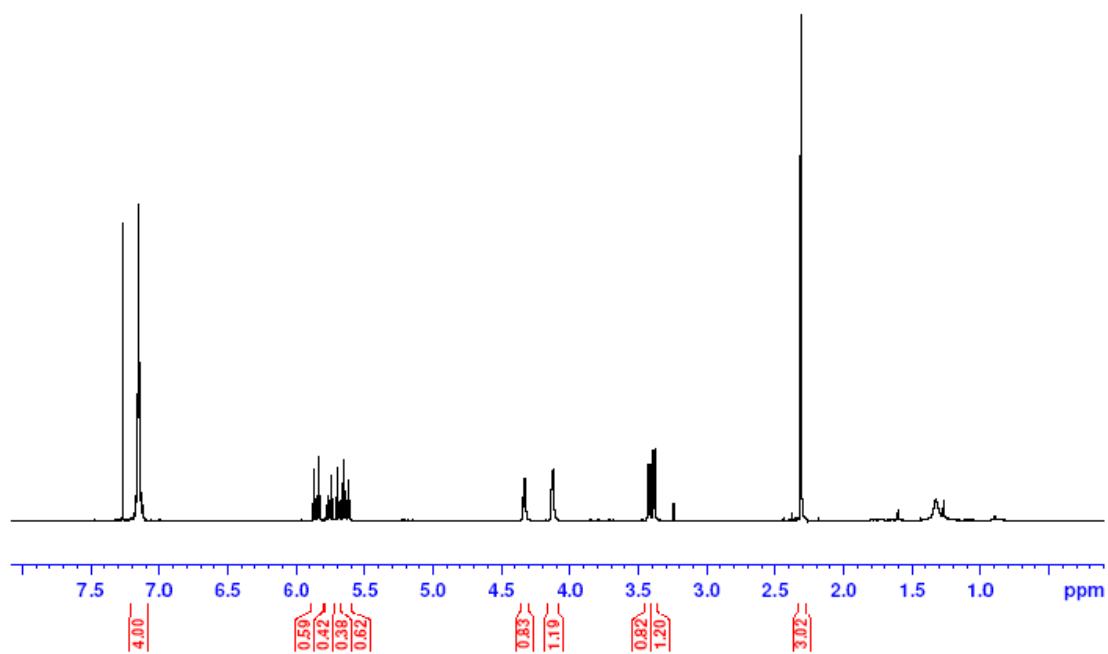


5.6

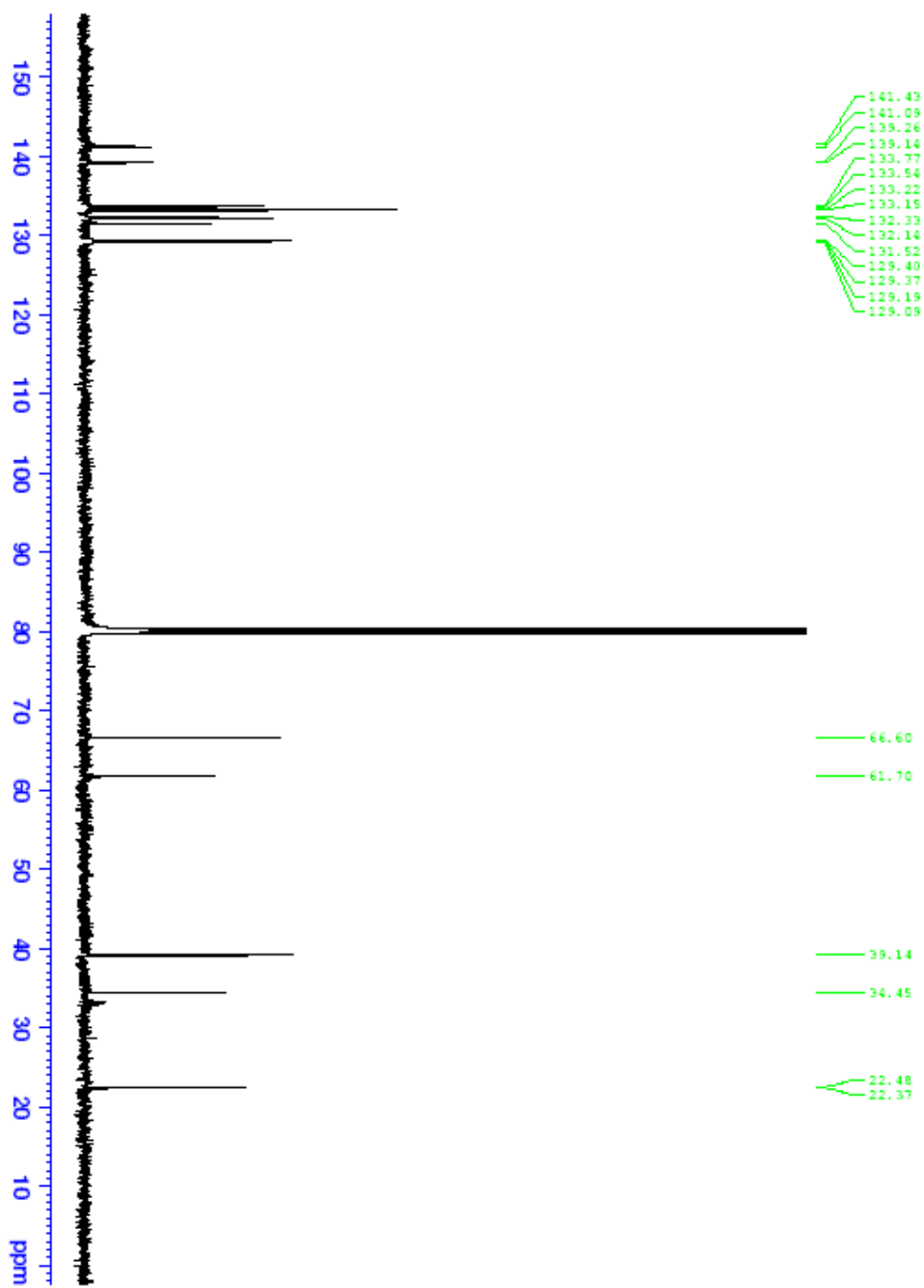
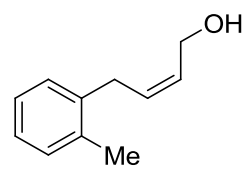
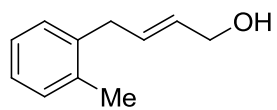


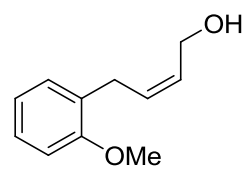
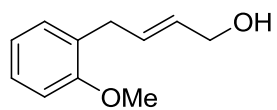


5.7



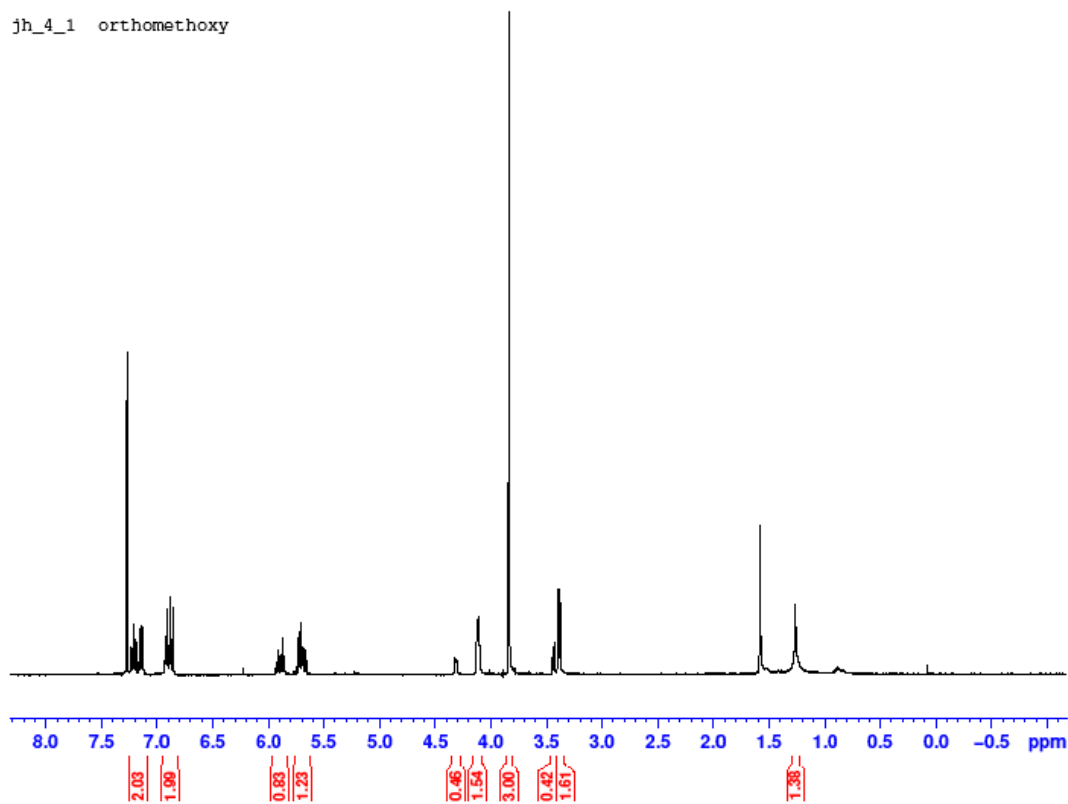


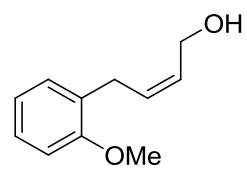
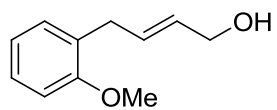




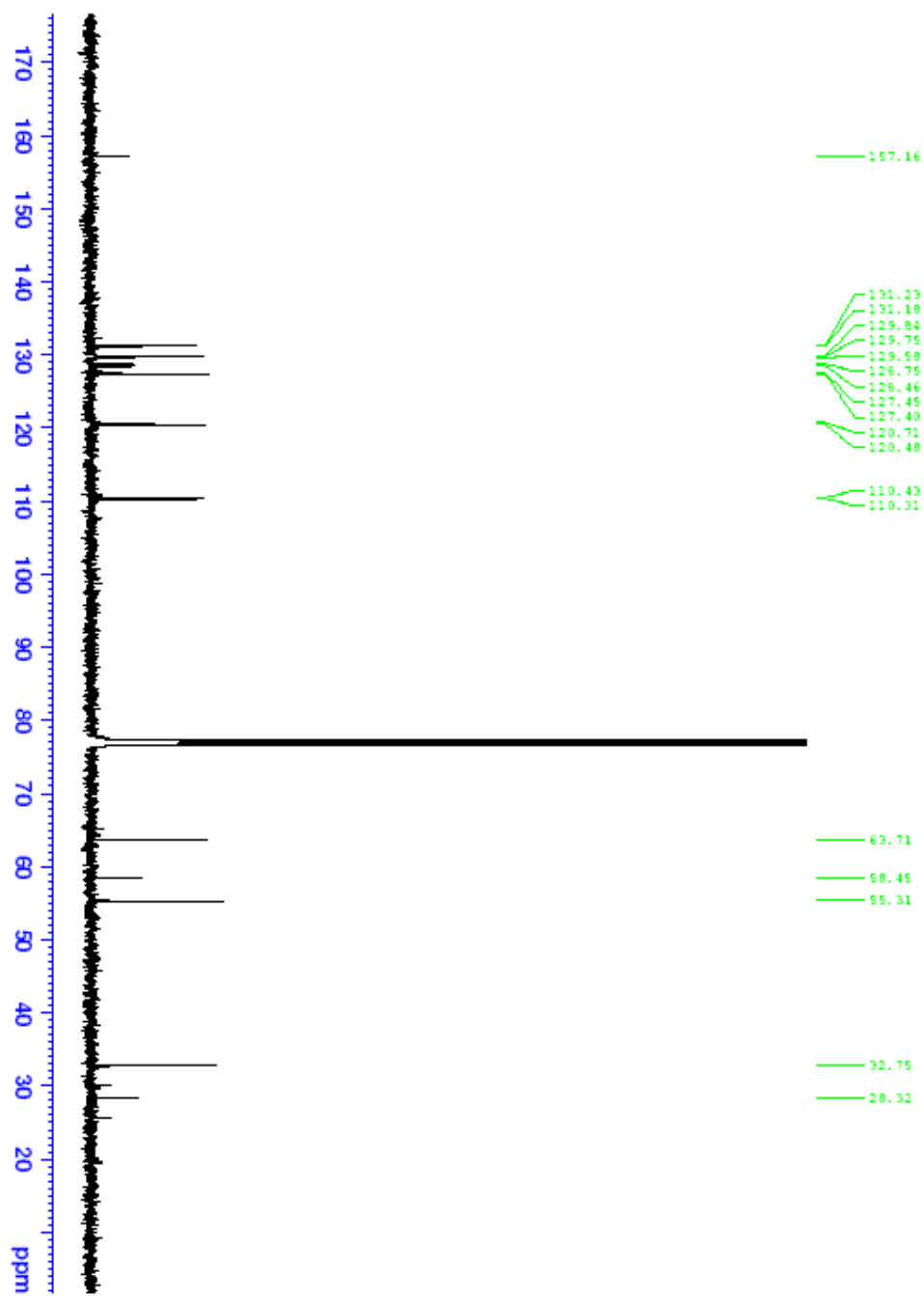
5.8

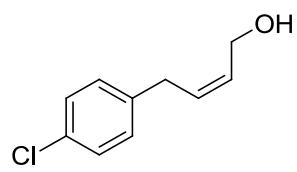
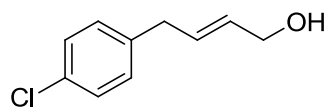
jh\_4\_1 orthomethoxy



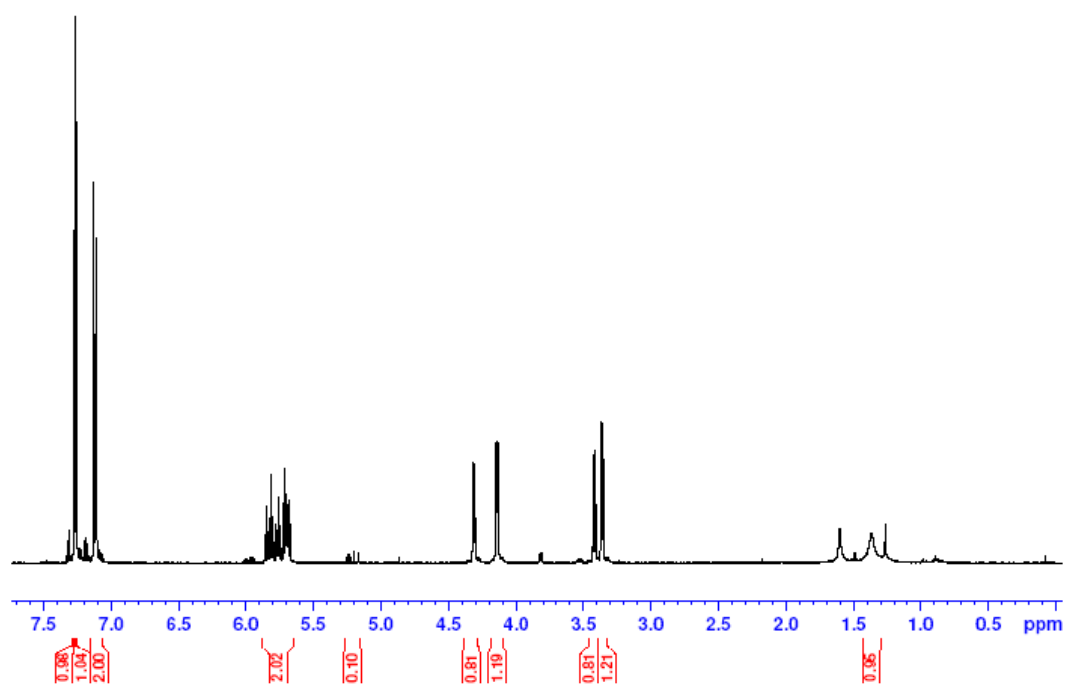


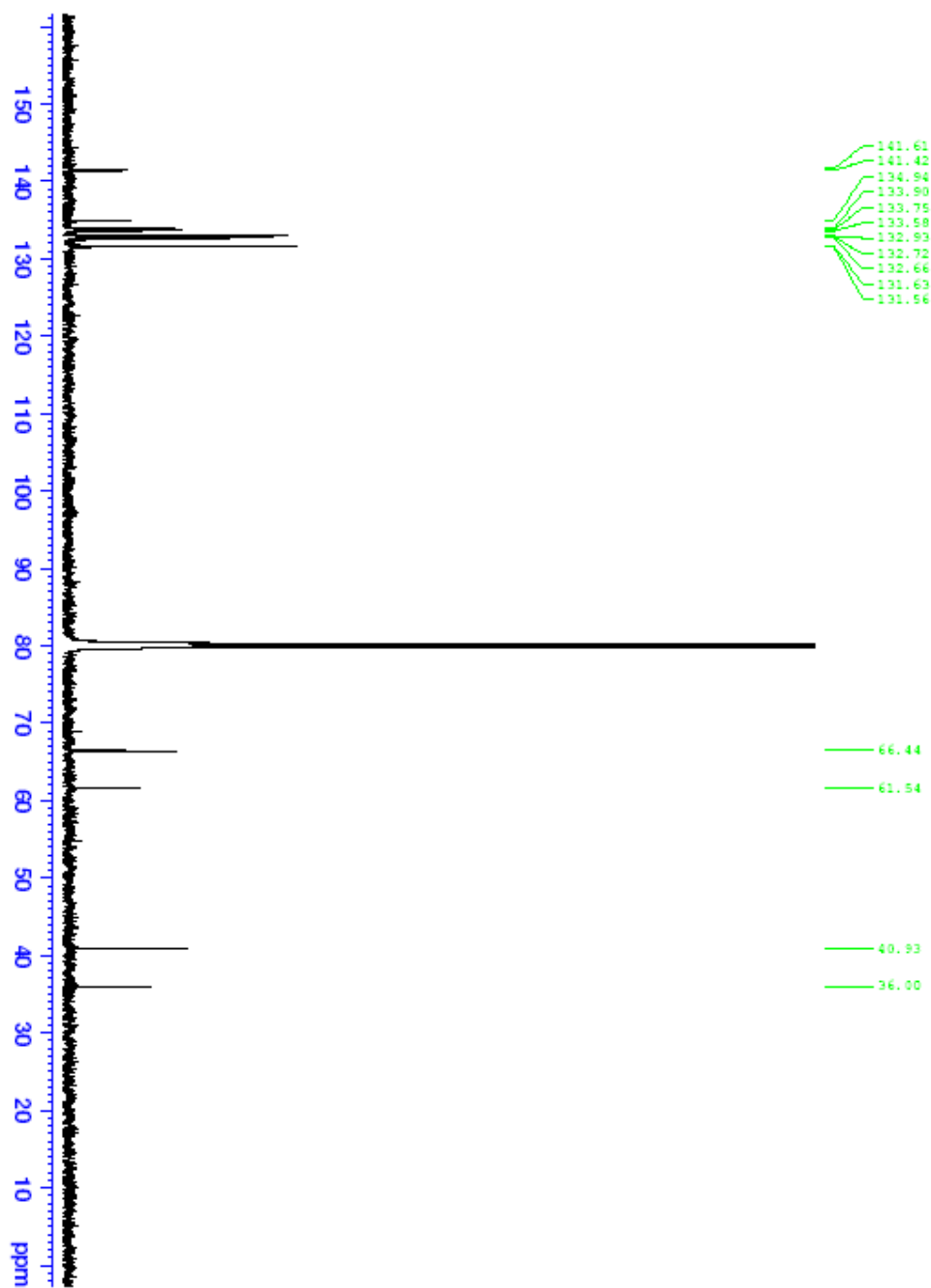
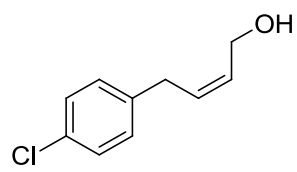
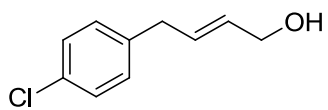
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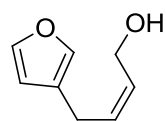
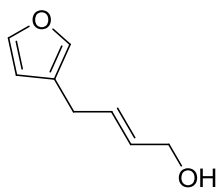




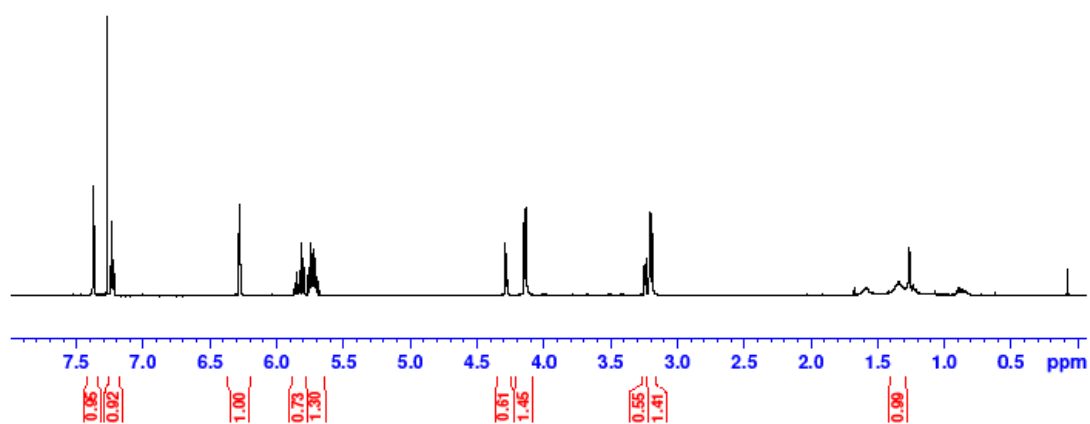
5.9

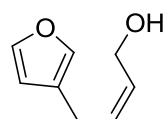
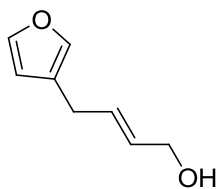




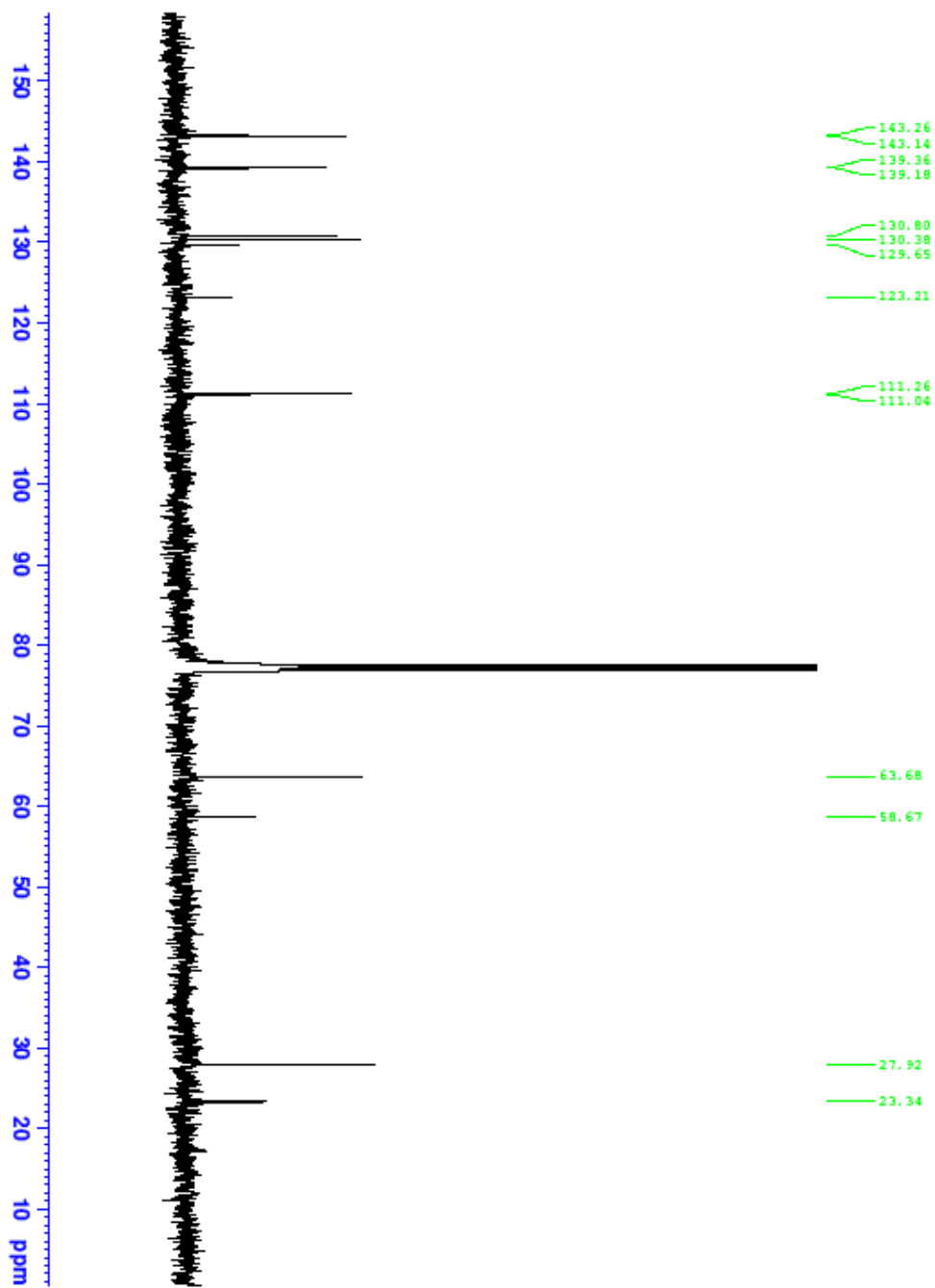


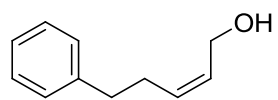
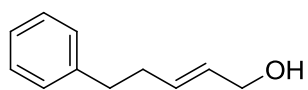
5.10



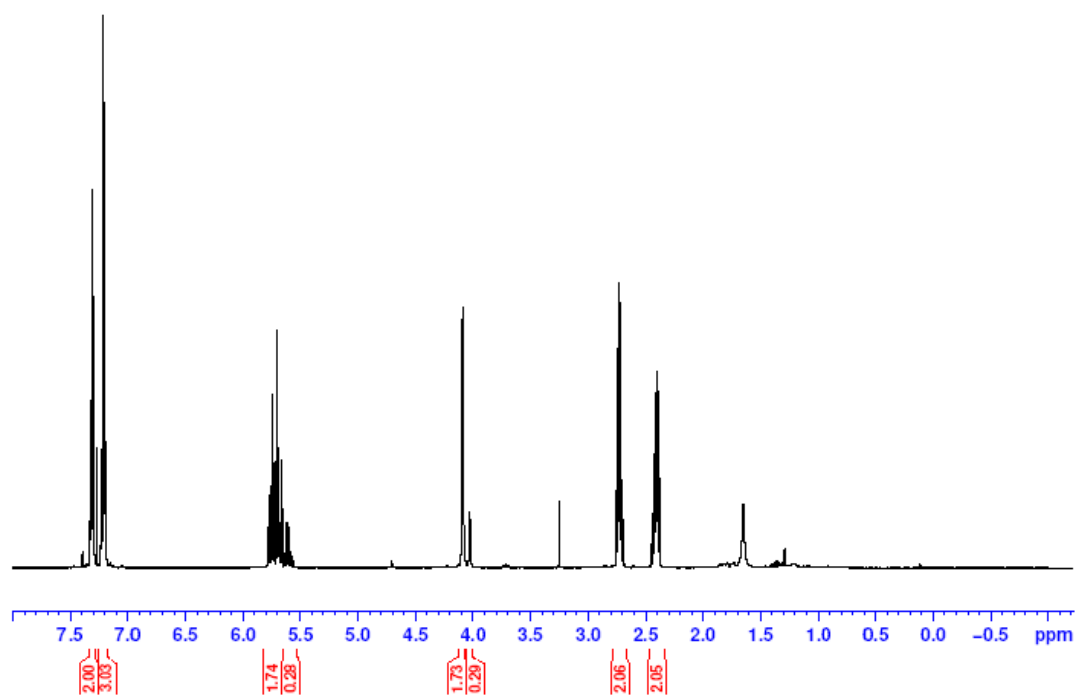


5.10

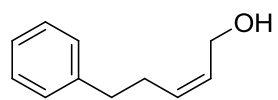
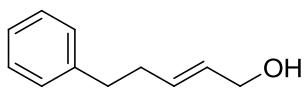




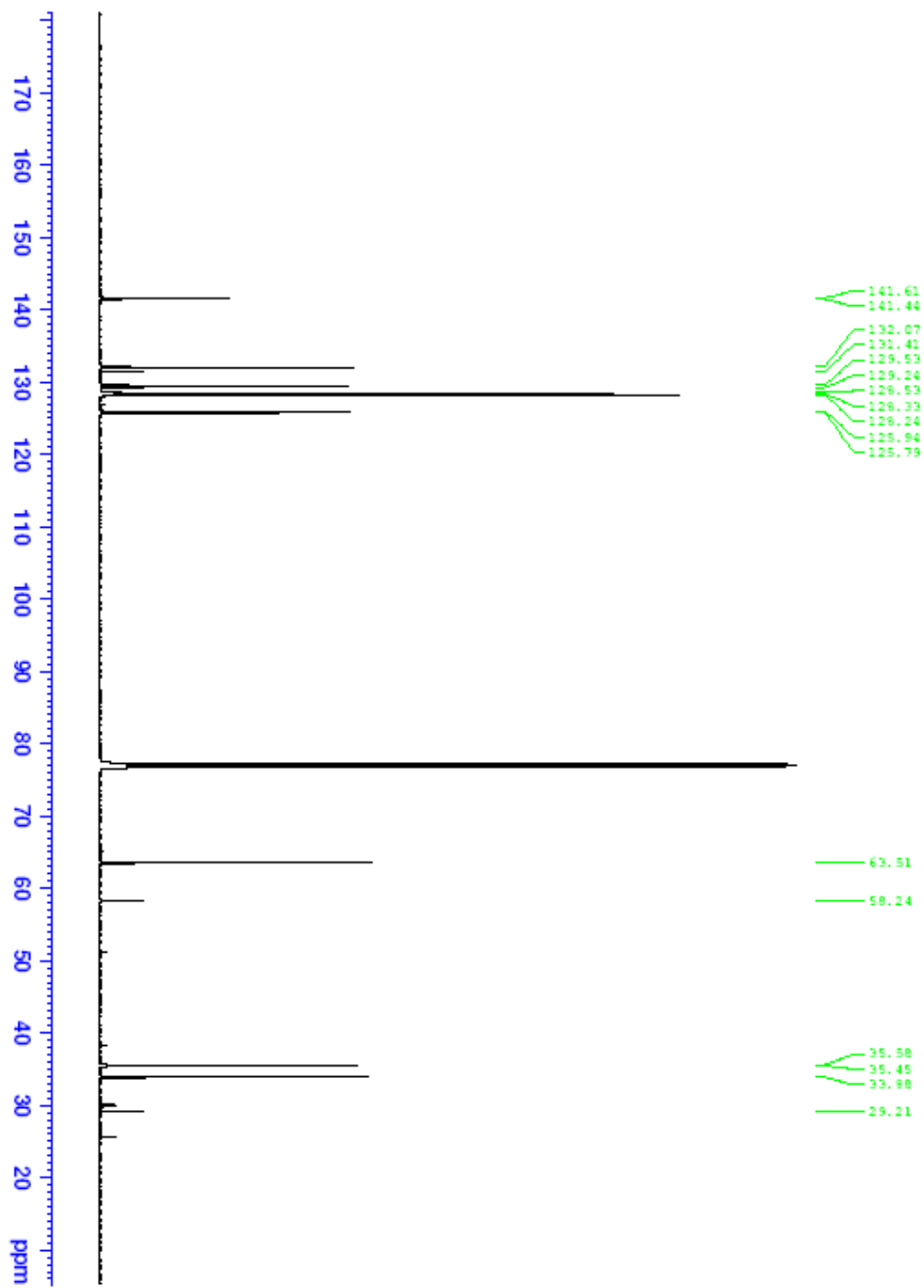
5.11

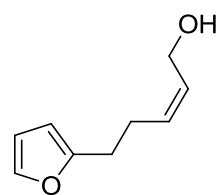
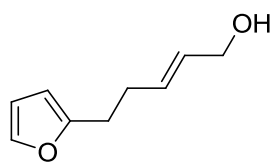




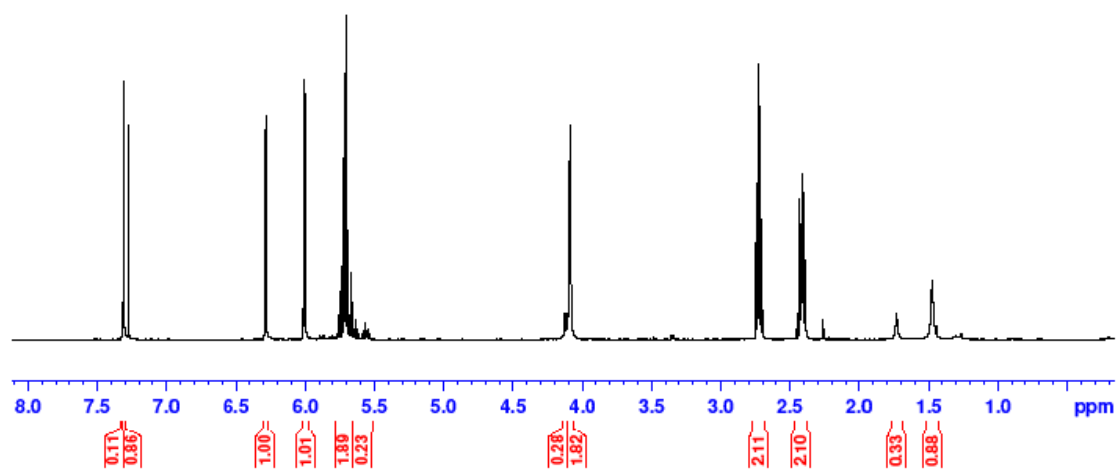


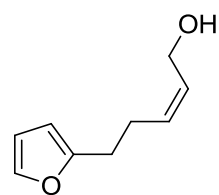
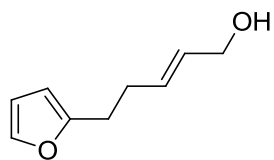
5.11



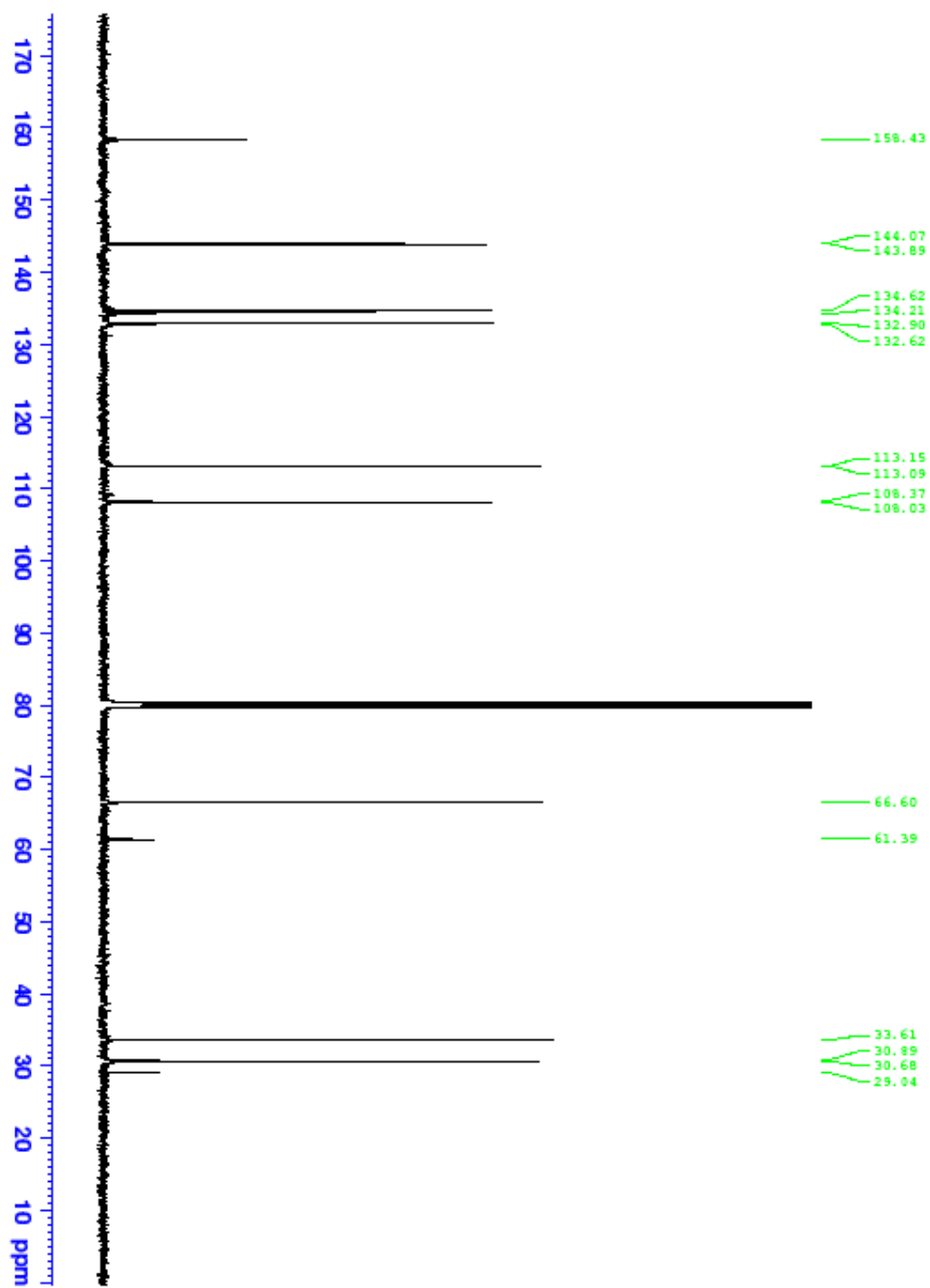


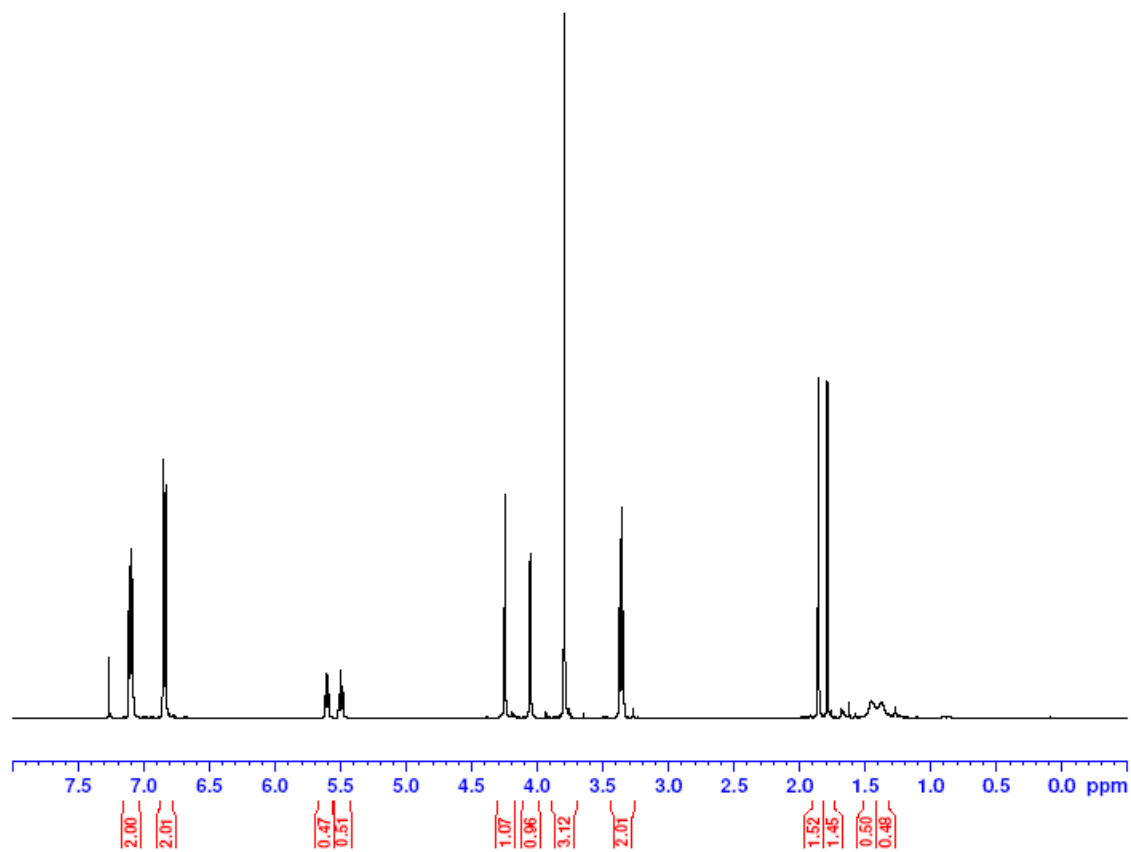
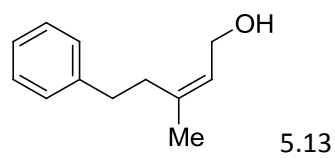
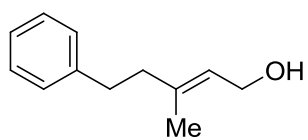
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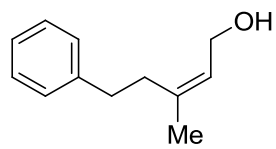
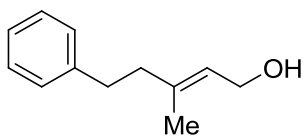




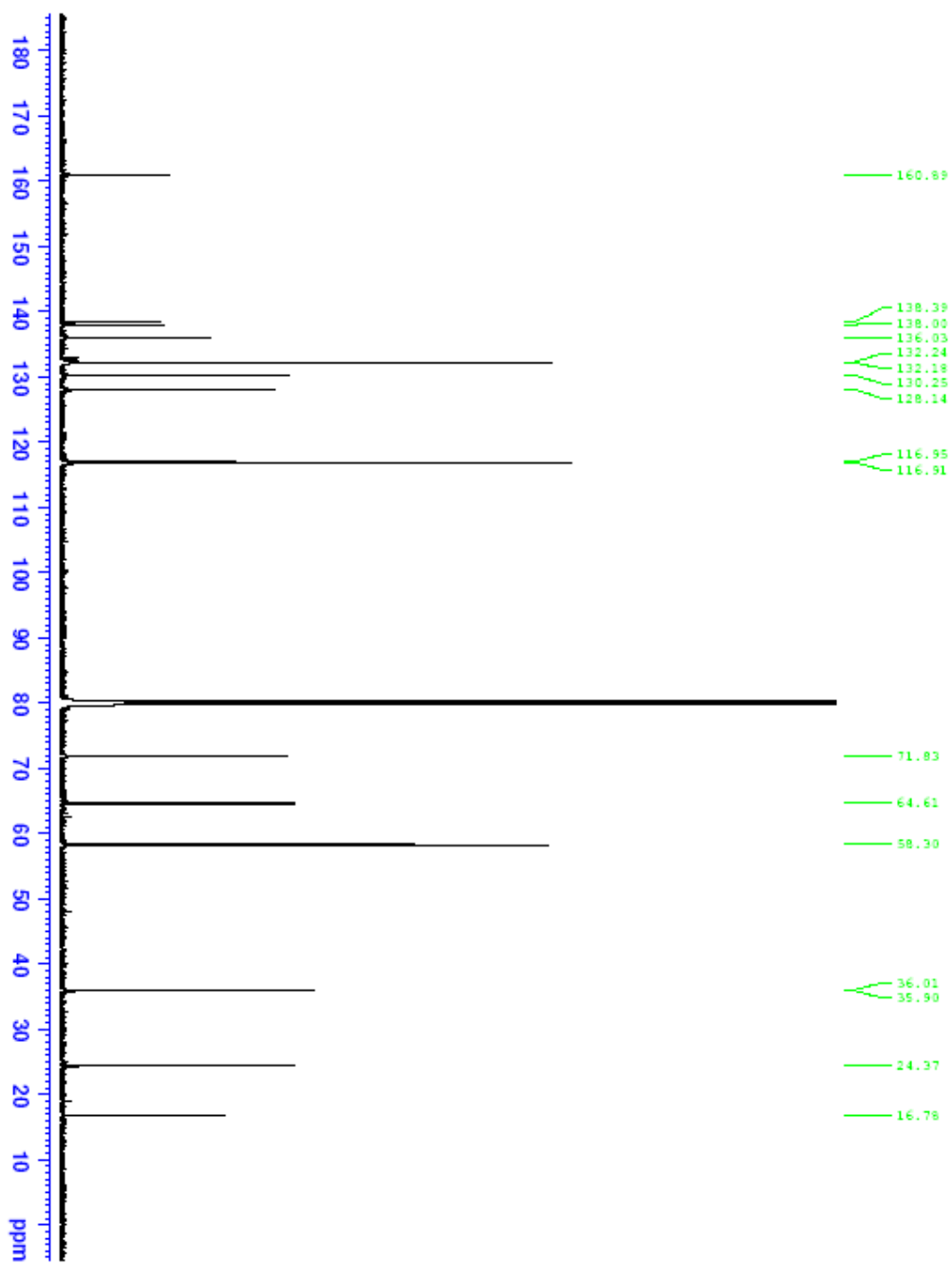
5.12

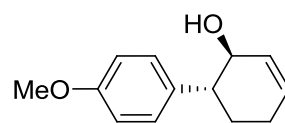
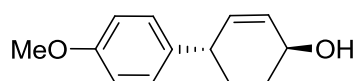




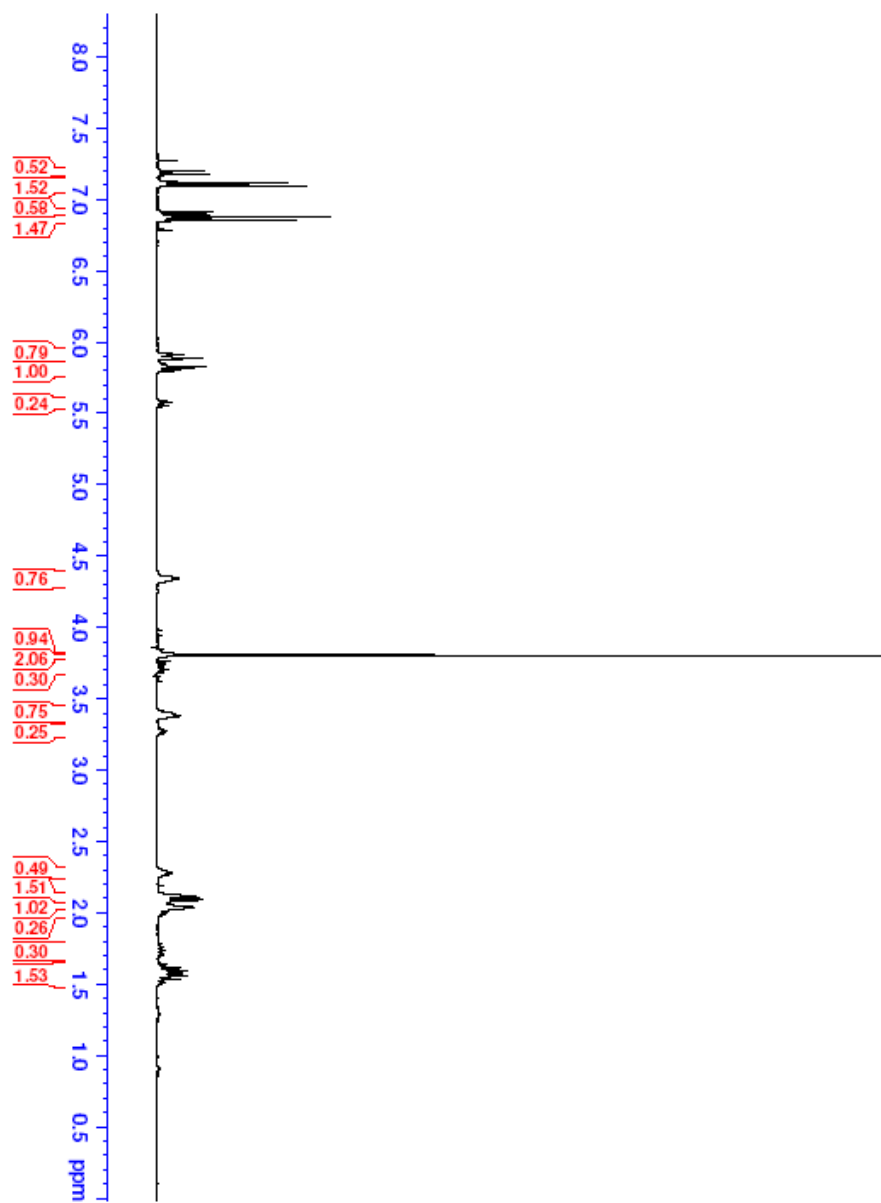


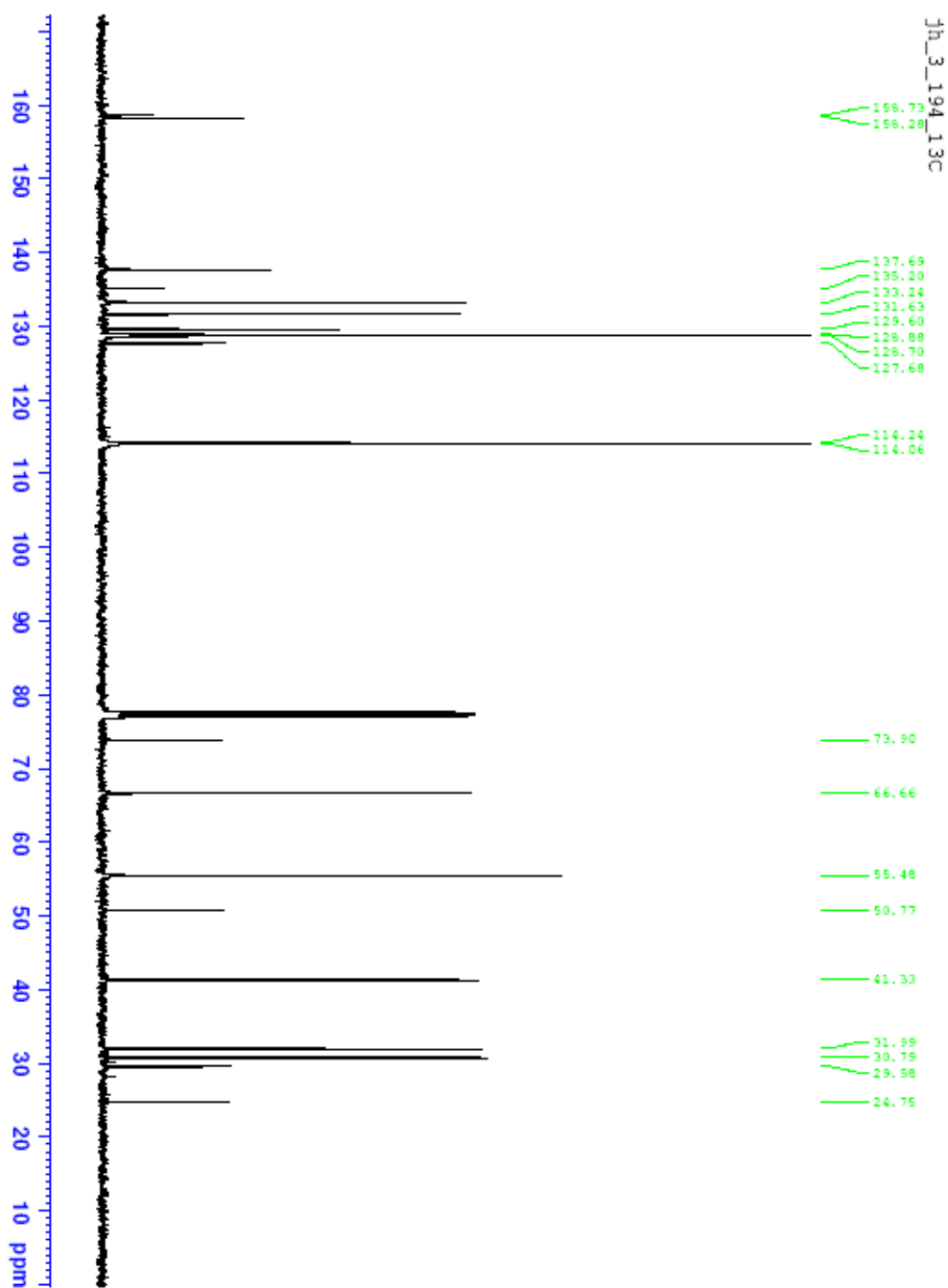
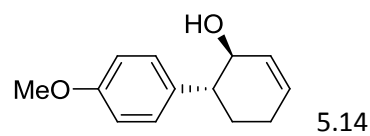
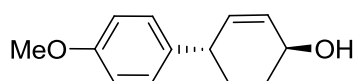
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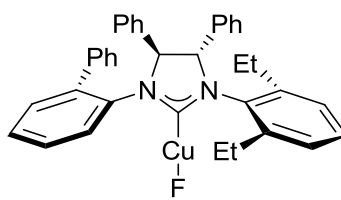




5.14

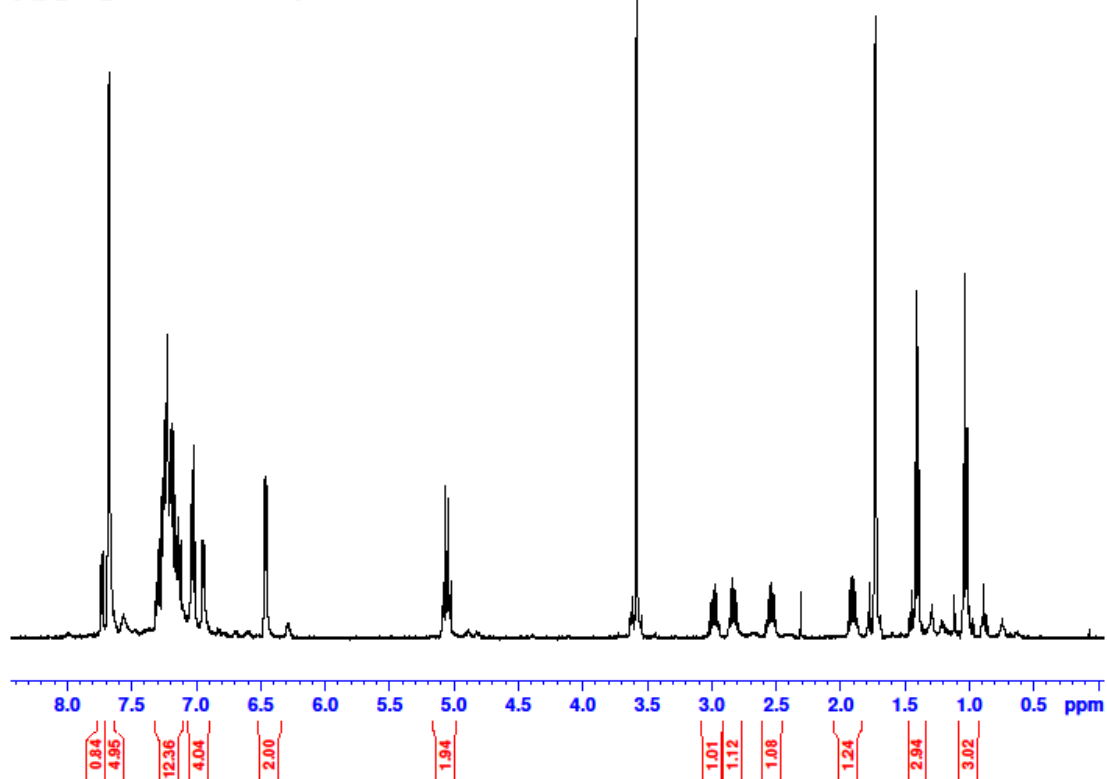




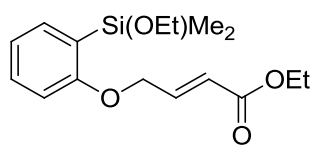


5.15

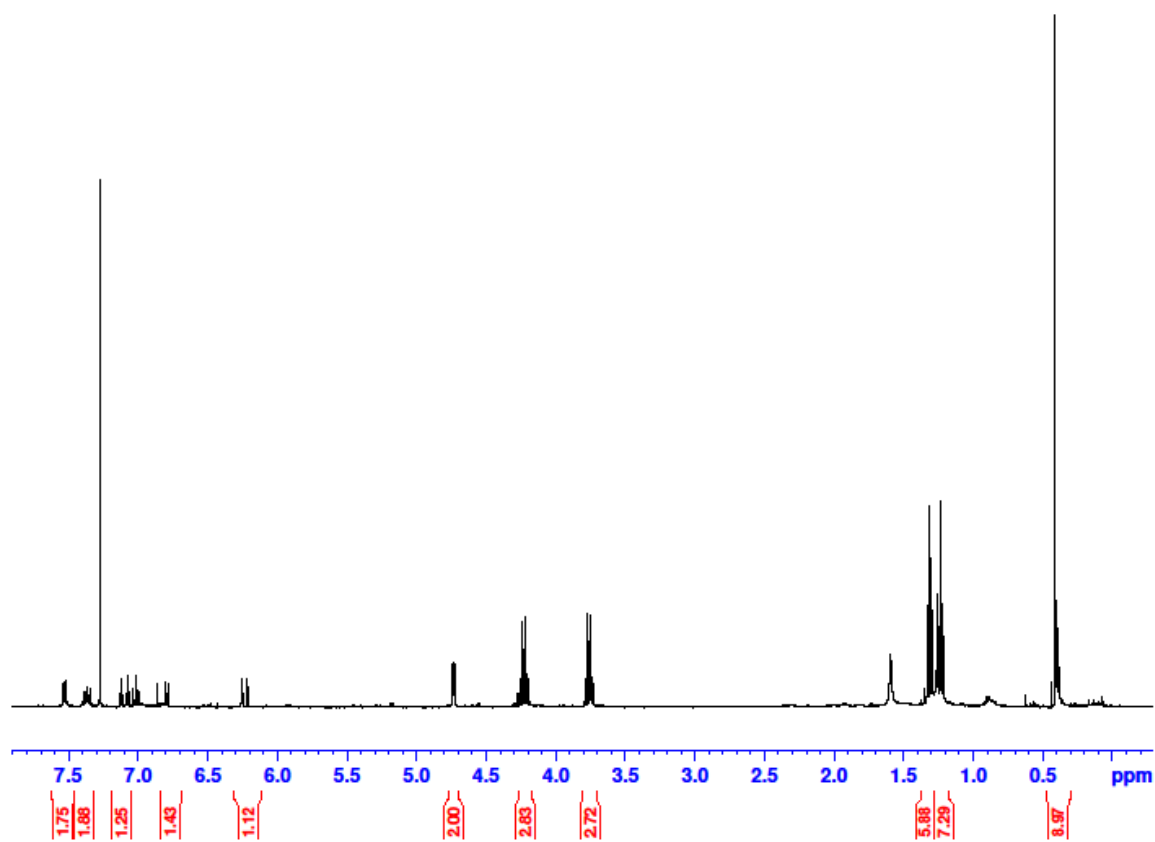
jh\_4\_149\_12-09-2009 14 mg of Cu in 500 microL of THF-d8

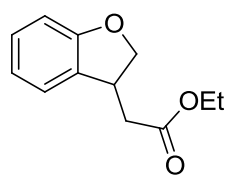




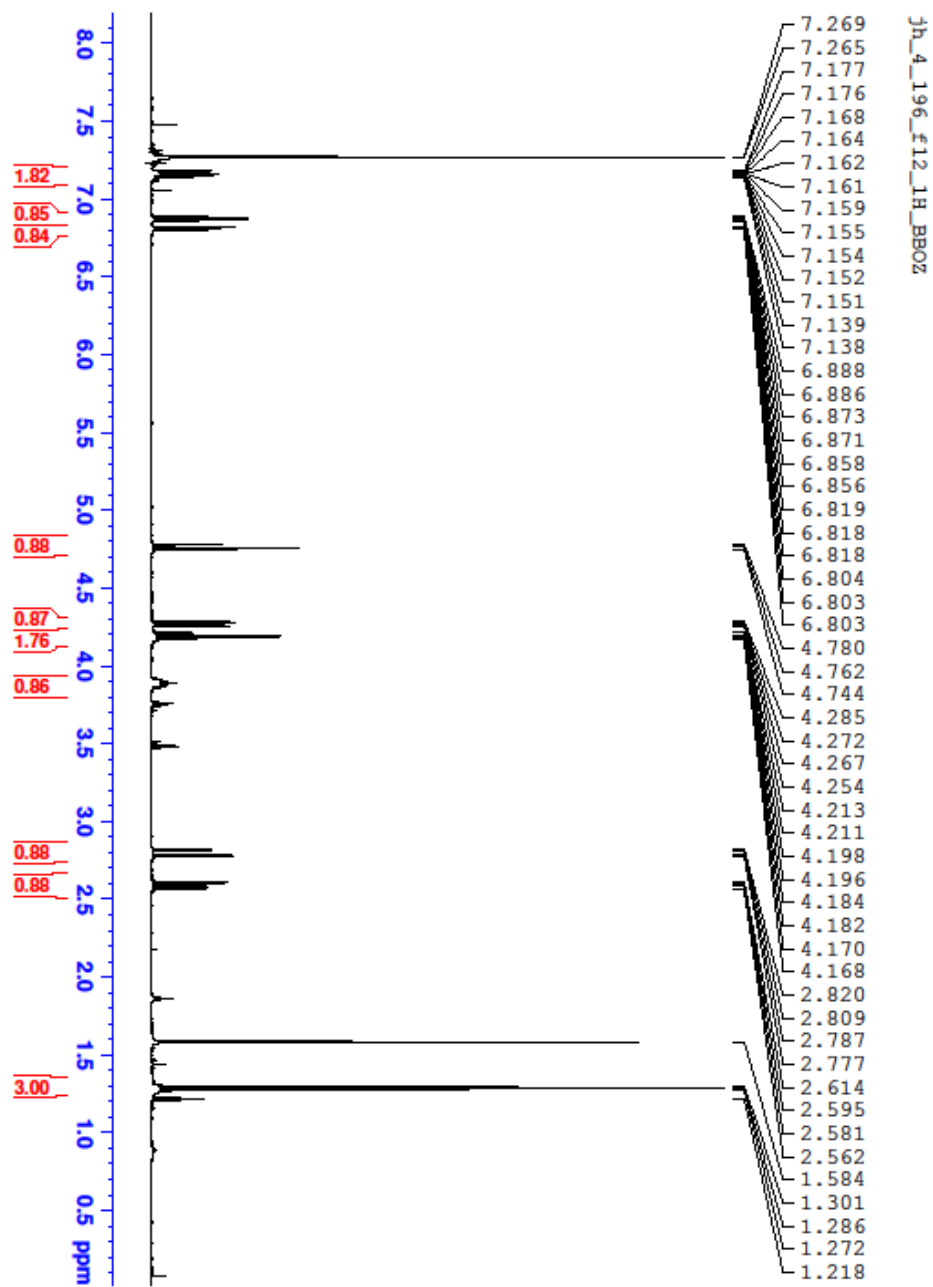


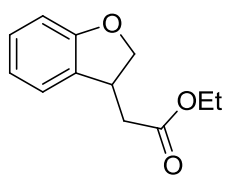
5.16





5.17





5.17

